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Nudelman

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(54) **METHODS OF IDENTIFYING GLYCOPEPTIDES RECOGNIZED BY DISEASE-ASSOCIATED AUTO-ANTIBODIES**

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CPC ***G01N 33/53*** (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

Methods for identifying glycopeptides and more particularly glycopeptide epitopes that are specifically recognized by disease-associated auto-antibodies are provided. In some aspects the auto-antibodies are cancer-associated or autoimmune disease associated. In other aspects, methods of diagnosing a patient with cancer or an autoimmune disease, or for eliciting an immune response in a mammalian host directed to the glycopeptides of the invention are provided.

3 Claims, 8 Drawing Sheets

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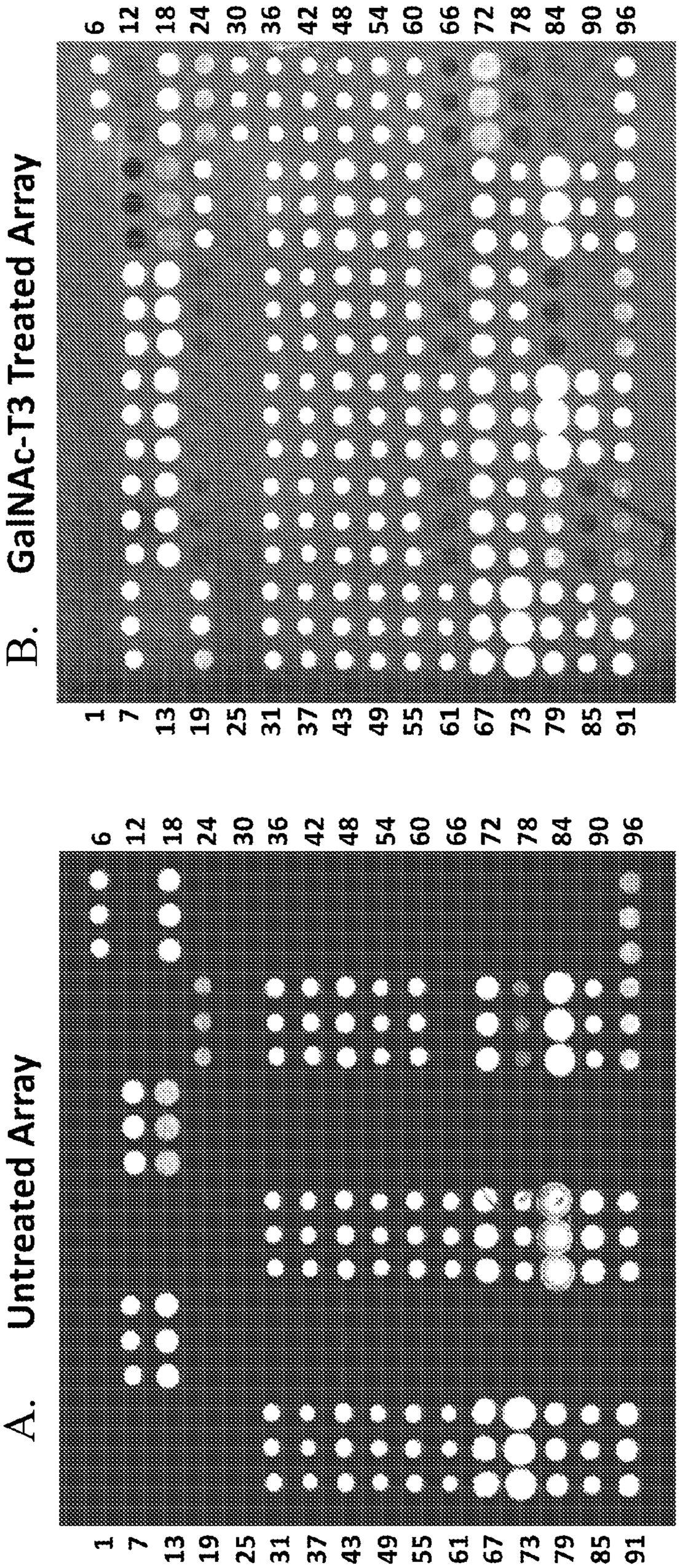
FIG. 1


A. Untreated Array
B. GalNAc-T3 Treated Array
1 7 13 19 25 31 37 43 49 55 61 67 73 79 85 91
6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96

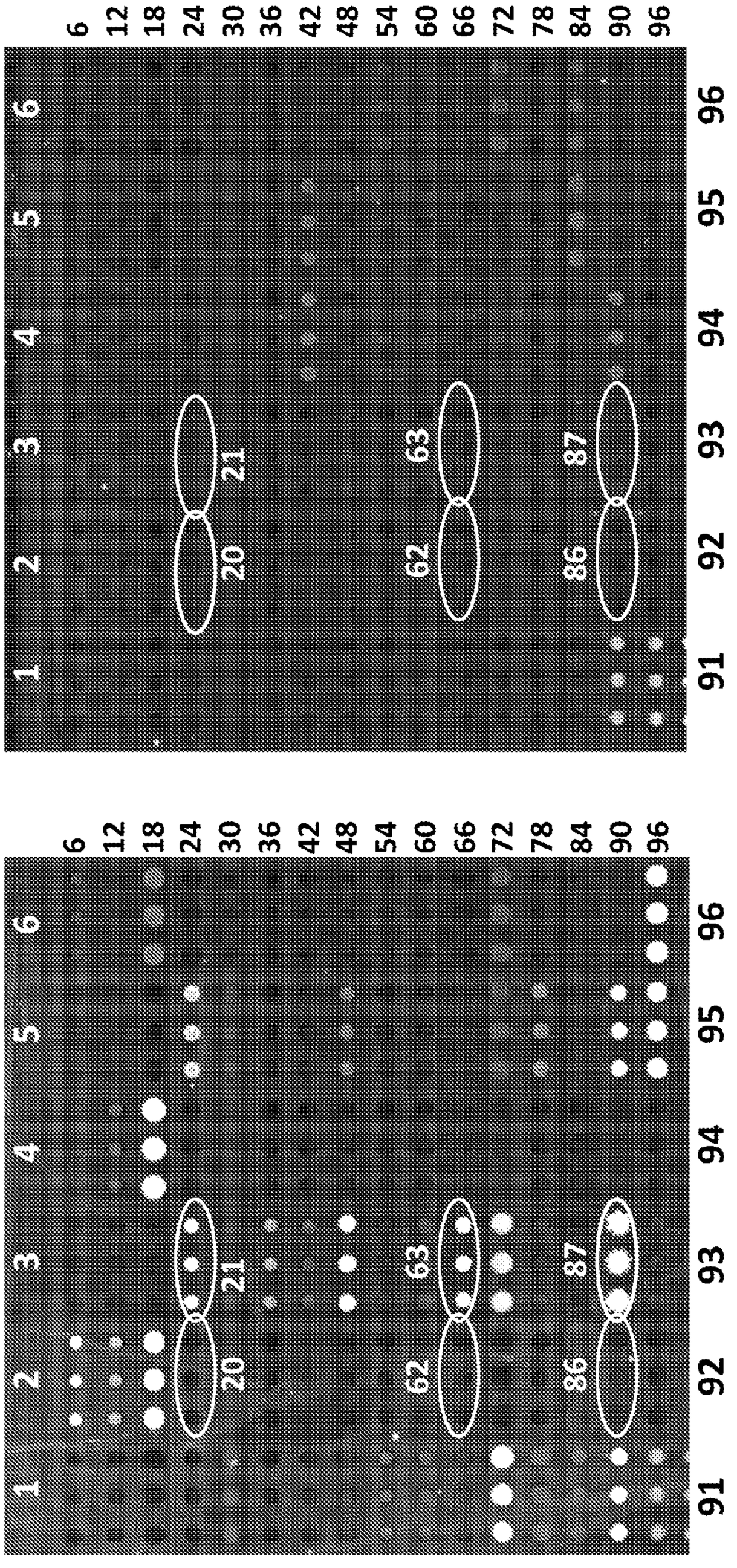

A. Prostate Cancer Serum #762
B. Normal Serum #174
6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96
1 2 3 4 5 6
20 21
62 63
86 87
91 92 93 94 95 96

FIG. 2

FIG. 3

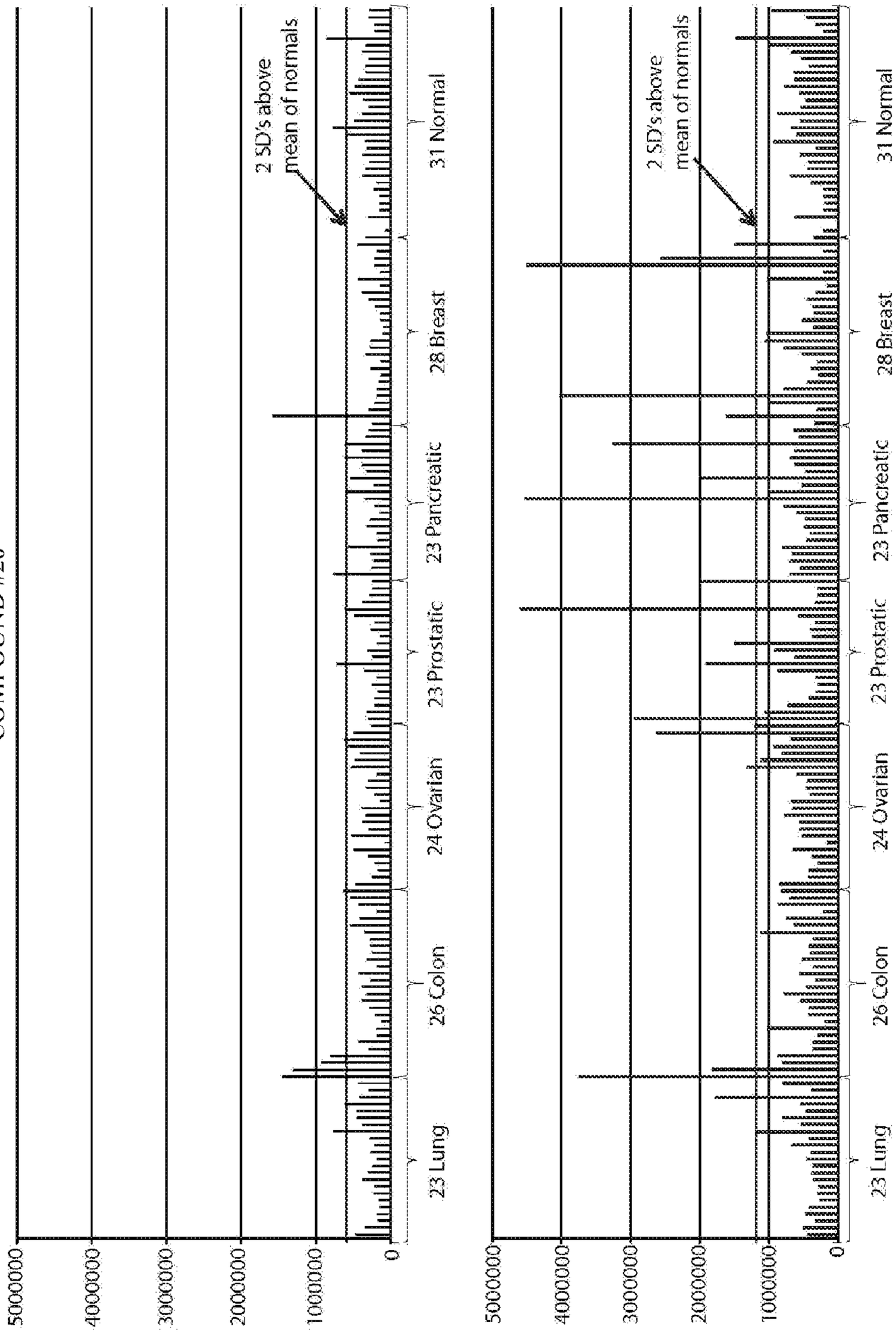

COMPOUND #20
5000000
4000000
3000000
2000000
1000000
0
23 Lung
26 Colon
24 Ovarian
23 Prostatic
23 Pancreatic
28 Breast
31 Normal
2 SD's above mean of normals
COMPOUND #21

FIG. 4

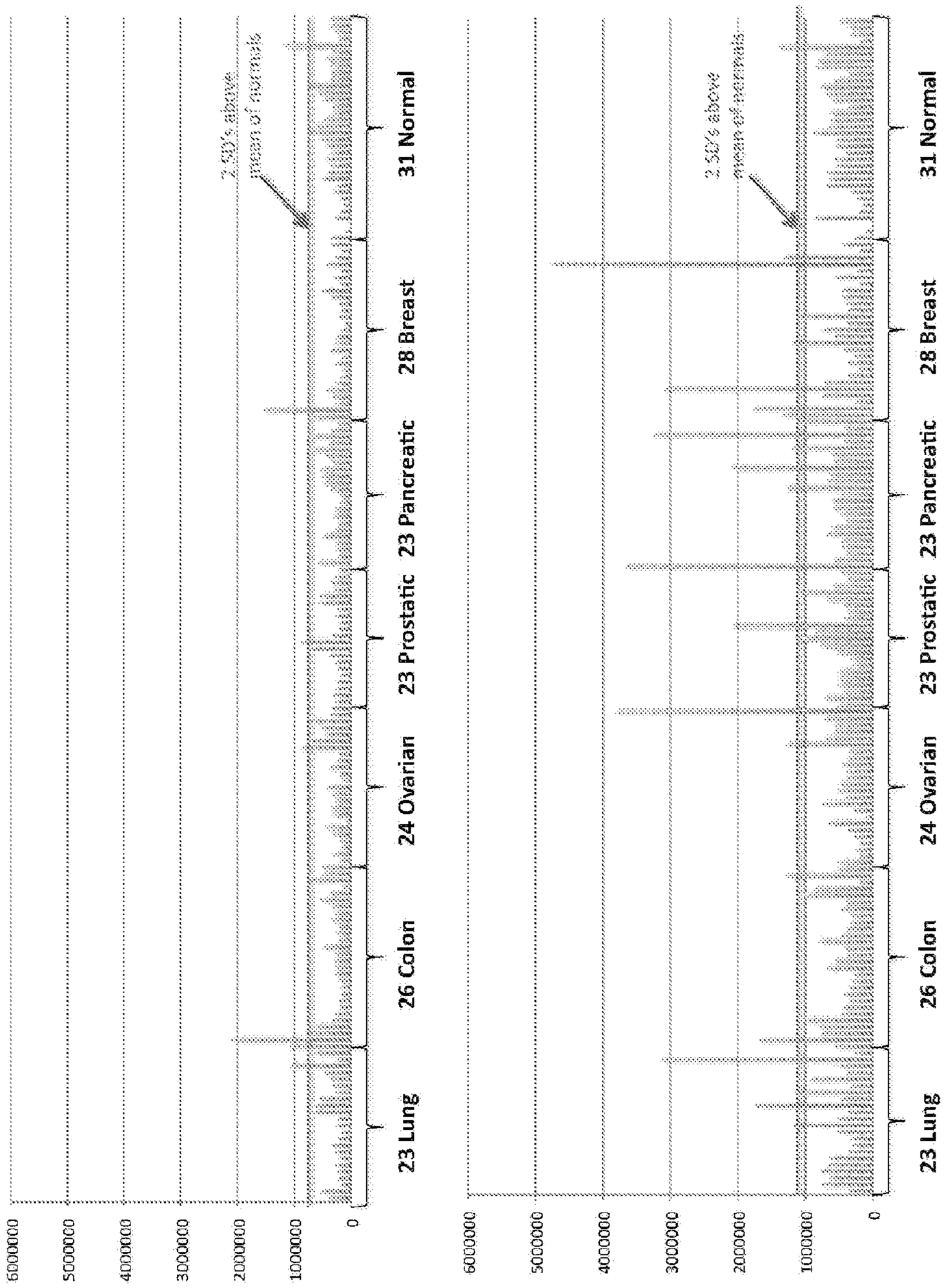

COMPOUND #62
2.5SD's above mean of normals
6000000
5000000
4000000
3000000
2000000
1000000
0
26 Colon
24 Ovarian
23 Prostatic
23 Pancreatic
28 Breast
23 Lung
31 Normal
COMPOUND #63
2.5SD's above mean of normals
6000000
5000000
4000000
3000000
2000000
1000000
0
26 Colon
24 Ovarian
23 Prostatic
23 Pancreatic
28 Breast
23 Lung
31 Normal

FIG. 5

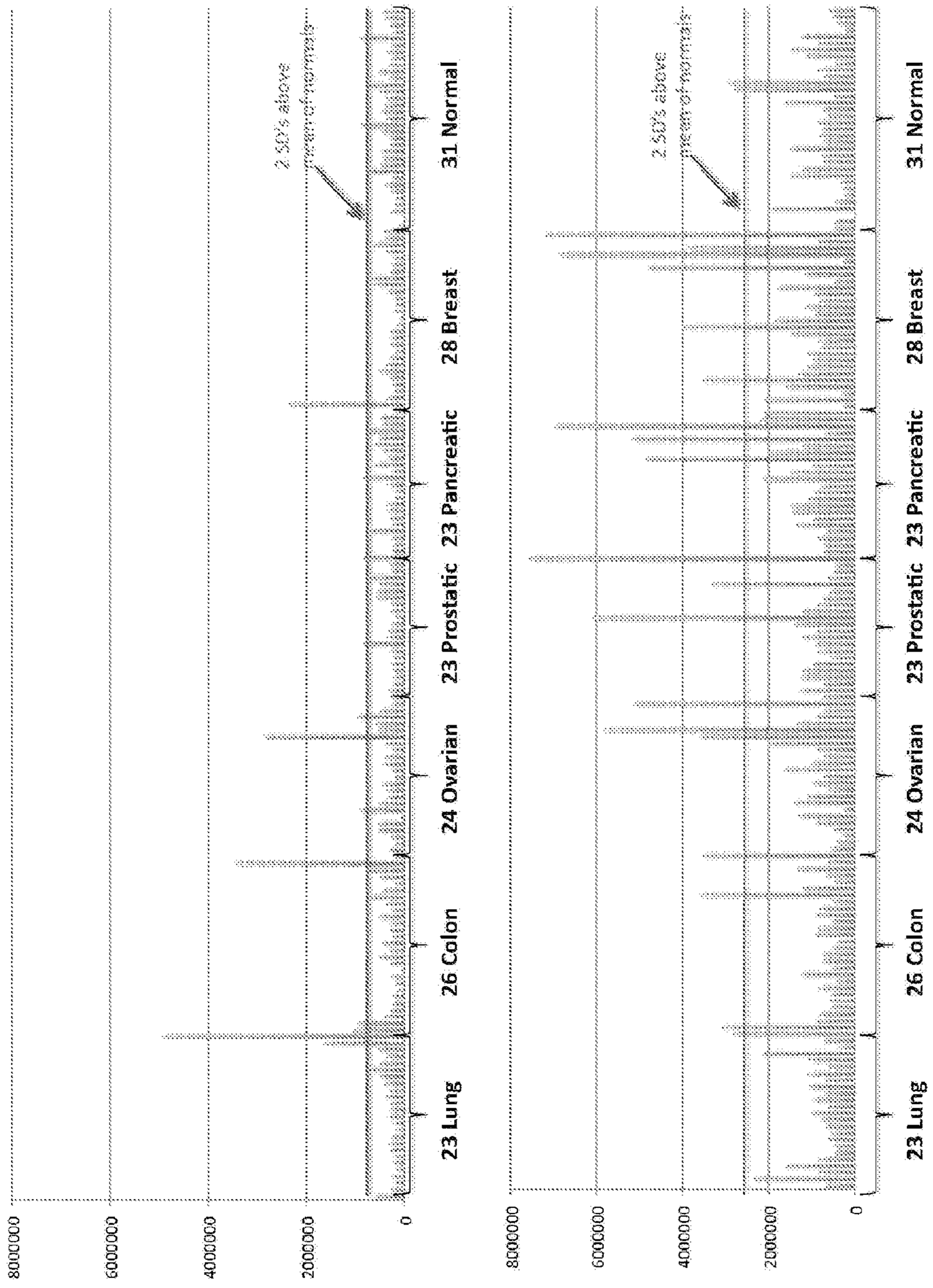

COMPOUND #86
2 SD's above mean of normals
31 Normal
28 Breast
23 Pancreatic
23 Prostatic
24 Ovarian
26 Colon
23 Lung
8000000
6000000
4000000
2000000
0
COMPOUND #87
2 SD's above mean of normals
31 Normal
28 Breast
23 Pancreatic
23 Prostatic
24 Ovarian
26 Colon
23 Lung
8000000
6000000
4000000
2000000
0

FIG. 6A

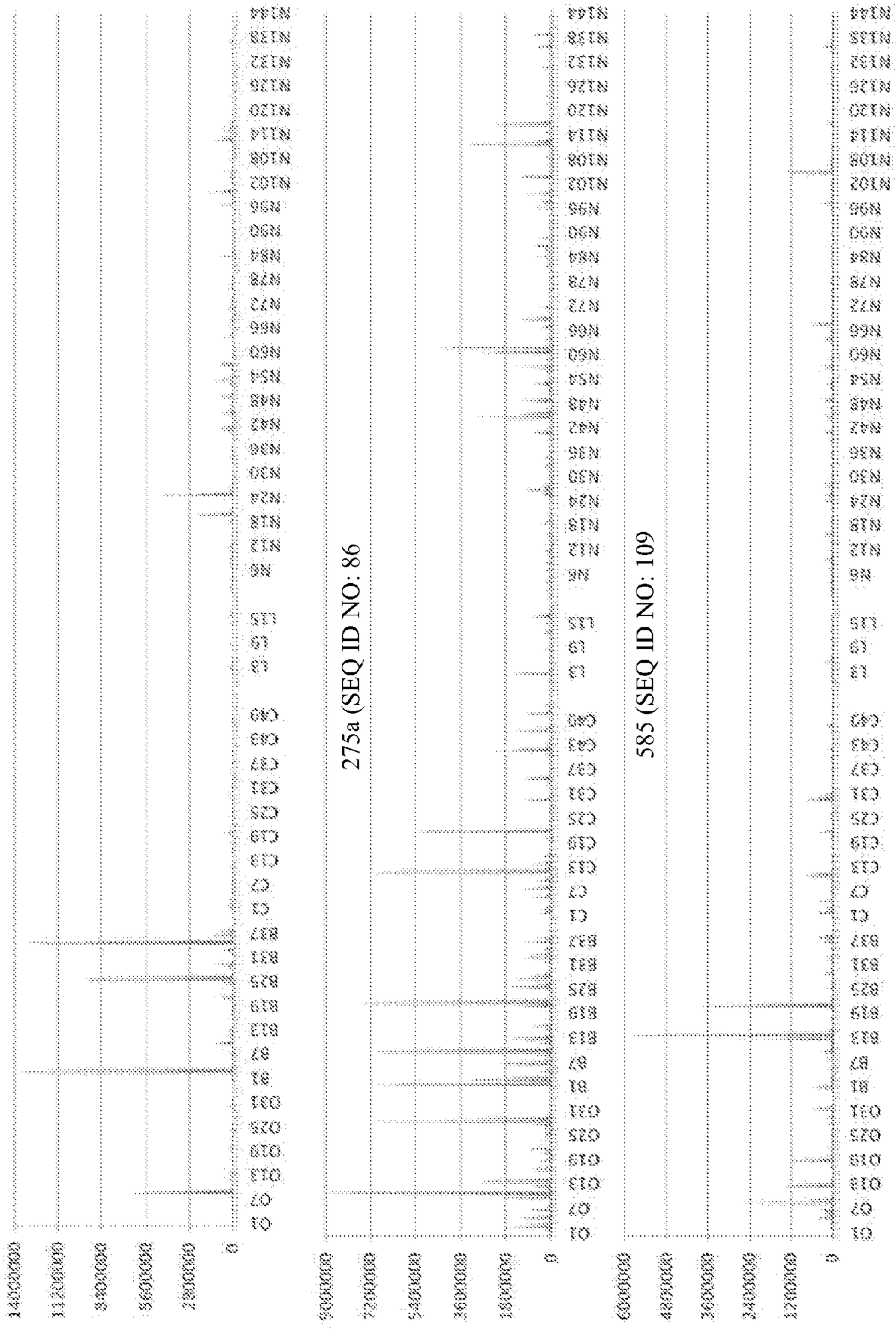


FIG. 6B

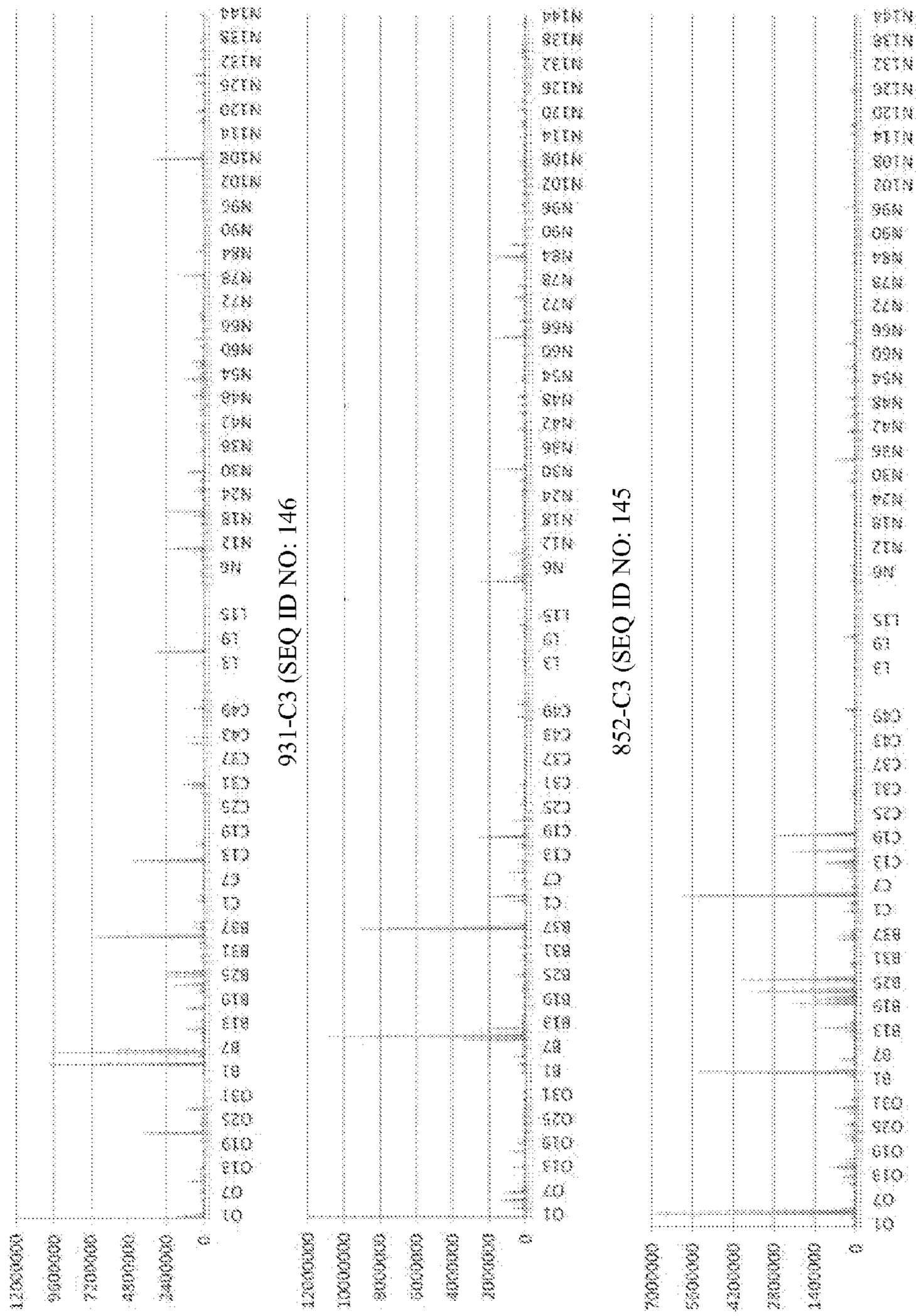
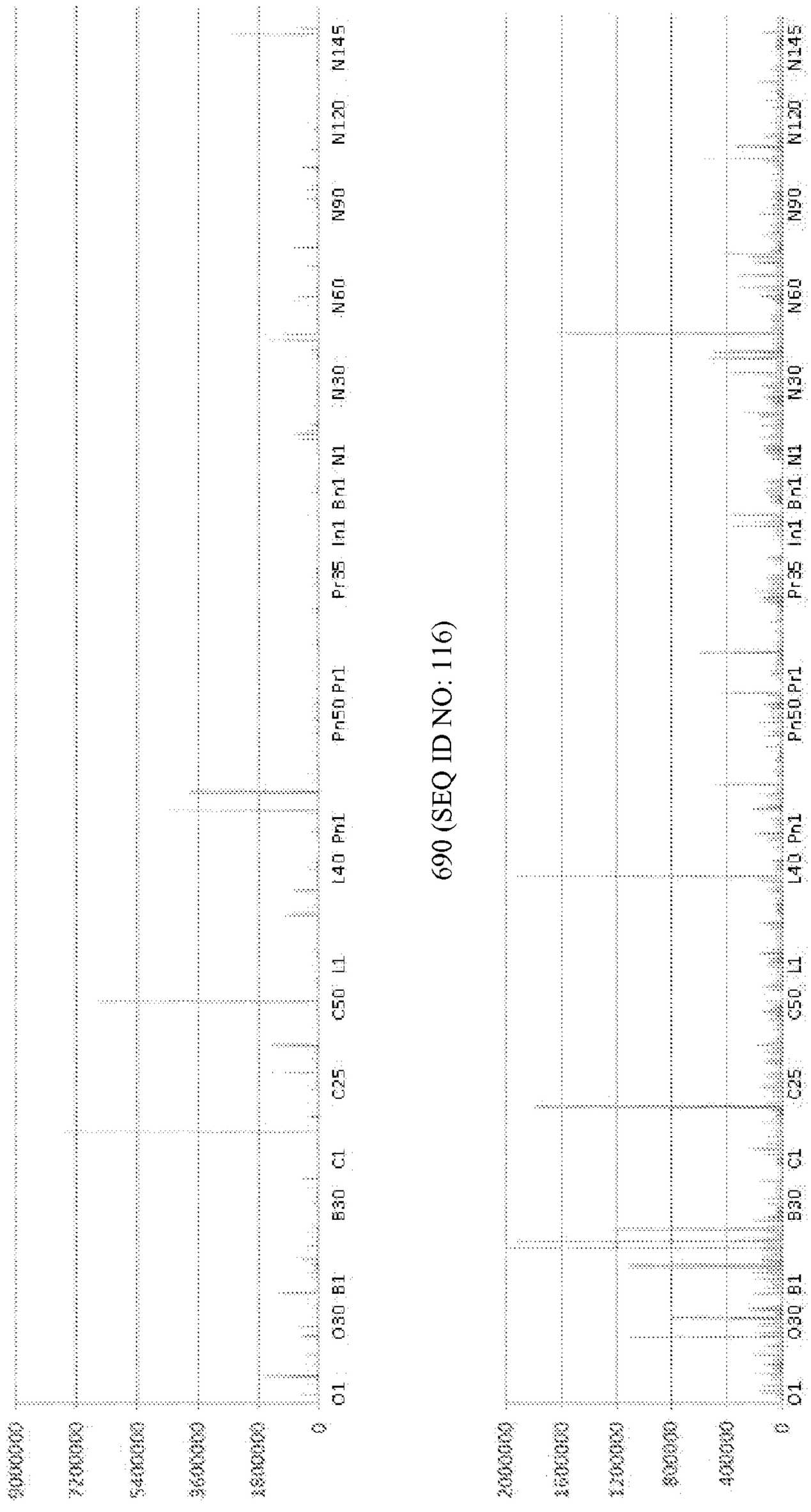


FIG. 6C


873 (SEQ ID NO: 132)
690 (SEQ ID NO: 116)
O1
O30
B1
B30
C1
C25
L40
Pn1
Pn50
Pr1
Pr35
In1
Bn1
N1
N60
N90
N120
N145
0
1000000
2000000
3000000
4000000
5000000
6000000
7000000
8000000

METHODS OF IDENTIFYING GLYCOPEPTIDES RECOGNIZED BY DISEASE-ASSOCIATED AUTO-ANTIBODIES

CROSS REFERENCE TO PRIOR APPLICATION

This application claims the benefit of U.S. Provisional Application Ser. No. 61/293,583 filed Jan. 8, 2010 and 61/294,477 filed Jan. 12, 2010, both of which are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

The present invention is related to methods for identifying glycopeptides and more particularly glycopeptide epitopes that are specifically recognized by disease-associated auto-antibodies. In some aspects the auto-antibodies are cancer-associated or autoimmune disease-associated. The invention also relates to methods of diagnosing a patient with cancer or an autoimmune disease, or for eliciting an immune response in a mammalian host directed to a glycopeptide of the invention. The invention also relates to novel individual glycopeptides as well as to panels of glycopeptides (whether individually novel or not) useful for autoantibody detection purposes.

BACKGROUND OF INVENTION

Malignant transformation of cells is virtually always accompanied by alterations in the posttranslational modifications (PTMs) of proteins, and one of the best documented examples is the abundant mucin-type O-glycosylation (hereafter referred to as O-glycosylation) found on mucins and other O-glycoproteins (Tarp and Clausen 2008). Tumor-associated changes in expression of O-glycoproteins and/or in their aberrant glycosylation, create a diverse set of unusual molecular structures found on the surface of cancer cells as well as in secretions. These molecular structures generally represent glycoproteins with truncated immature O-glycans, to which the immune system of man is not normally exposed except, in some cases, as biosynthetic intermediates and then only in the secretory pathway. Therefore, these structures may represent a different form of tumor-associated antigens (one not necessarily based on differential expression level or sequence mutation), to which individuals lack immunological tolerance and thus provoke both auto-antibodies and cell mediated immunity (Anderton 2004; Doyle and Mamula 2005; Doyle and Mamula 2001).

Several mouse antibodies have been isolated and characterized as having unique binding specificity for combined glycopeptide epitopes that include both the peptide sequence as well as the aberrant PTM (hereinafter "APTM") for efficient binding. Examples include monoclonal antibodies that specifically recognize distinct O-glycopeptides from MUC2, MUC1, and other glycoproteins (Reis et al. 1998; Sorensen et al. 2006; Danielczyk et al. 2006; Dian et al. 2009; Li et al. 2009; Takeuchi et al. 2002; Clark et al. 1998).

There exist examples of human antibodies with selective or specific reactivity with PTM-modified proteins, but these are generally limited to inflammatory and autoimmune diseases (Anderton 2004; Doyle and Mamula 2005; Doyle and Mamula 2001). Furthermore, human hydridoma technologies have identified natural IgM antibodies that react with glycoforms of proteins but the nature of the epitopes has not been fully clarified (Rauschert et al. 2008; Vollmers and Brandlein 2009; Brandlein et al. 2004a; Brandlein et al. 2004b; Rasmussen and Ditzel 2009). A major drawback of current technologies to screen for auto-antibodies directed against APTM proteins is the lack of high through-put methods for identifying antigens, more particularly epitopes, for generating pertinent antigens and for screening such antigens.

In principle, cancer-associated auto-antibodies represent appealing potential biomarkers. Auto-antibodies may develop early in carcinogenesis, at the time tumor-associated antigens appear on premalignant or malignant lesions. Antibody responses can produce relatively high concentrations in circulation with a long circulation time, and they can be detected with sensitive and specific methods (see, (Lu et al. 2008; Anderson and Labaer 2005)). In contrast, antigens produced by small premalignant or malignant lesions are generally produced in vanishingly small levels that due to dilution and clearance from blood may not be detectable by conventional techniques. Discovery and characterization of specific auto-antibodies to cancer antigens have been undertaken using different approaches in the past. Classical studies identified such antibodies reactive with tumor cells, tissues, or isolated proteins (Kawabata et al. 2007), but distinct molecular features of binding epitopes have generally not resulted from these approaches.

More recent proteome-wide screening techniques have included expressed cDNA libraries (SEREX) (Sahin et al. 1995), protein and peptide arrays (Stockert et al. 1998; Pereira-Faca et al. 2007), random or designed phage displays (Mintz et al. 2003), and more recently self-assembling protein arrays (Ramachandran et al. 2008; Anderson et al. 2008). Cancer-associated auto-antibodies characterized to date have been found to bind intracellular proteins with functions important in cell cycle regulation, such as GPR78 (Mintz et al. 2003), p53 (Lubin et al. 1993), NY-ESO-1, and CDC25 (Liu et al. 2008), but also some cell membrane glycoproteins such as MUC1 (Snijdewint et al. 1999), HER2 (Chapman et al. 2007) and Mesothelin (Hellstrom et al. 2008).

Auto-antibodies are believed to be induced as a result of altered expression of proteins and altered molecular structure due to mutations, alternative splicing and post-translational events such as protein processing and aberrant enzymatic modifications including glycosylation (Anderton 2004; Doyle and Mamula 2005; Doyle and Mamula 2001). These events induce breakage of tolerance and immunity may result. Surprisingly, however, few disease- or more specifically cancer-associated auto-antibody epitopes have been identified and molecularly defined despite considerable efforts and broad proteome screening. This is due to limitations in methods for identification of such auto-antibodies, in that, before the present invention, the appropriate antigen epitopes have not been determined and hence not tested to lead to identification of disease-associated antibodies, to serve as substrates for the detection of disease or to serve as prototype vaccines for induction of immunity against the epitopes of these autoantibodies.

There are few known examples of disease-associated human antibodies to proteins involving glycosylation. One important example is an immunodominant epitope in type II collagen comprising a glycosylated hydroxylysine residue that is involved in collagen-induced arthritis (Backlund et al. 2002). Glycosylation may also modulate protein processing and hence affect exposure of new epitopes as shown in Rasmussen's encephalitis, where an N-glycan blocks proteolysis of a neuronal glutamate receptor and a short preceding peptide epitope (Gahring et al. 2001). Several human monoclonal antibodies have been shown to be directed to epitopes affected by glycosylation (Rauschert et al. 2008; Vollmers and Brandlein 2009; Brandlein et al. 2004a; Brandlein et al.

2004b; Rasmussen and Ditzel 2009), but the nature of the molecular epitopes remains undefined.

There is therefore a need to develop methods for the identification of PTM-containing peptides, such as aberrant glycopeptides (hereinafter "AGP"), that are specifically recognized by disease-associated auto-antibodies. The present invention provides such methods. There is also a need for improved diagnostic tools, such as AGP, that would permit early detection of disease, notably cancer, for example by being used as substrates to capture disease-associated autoantibodies.

SUMMARY OF INVENTION

In one embodiment, the invention provides a method for identifying glycopeptides reactive with cancer-associated auto-antibodies, the method comprising: providing a panel comprising peptides, at least a plurality of the peptides comprising one or more sites amenable to glycosylation, wherein at least one of the glycosylation sites has been modified with a glycan to form a glycopeptide having a peptide portion and a glycan portion; contacting the panel with an antibody-containing sample from a patient with cancer; and identifying glycopeptides in the panel that (i) are selectively recognized by antibodies in the sample, but not by antibodies in a control sample and (ii) are recognized by such antibodies in the sample through recognition of both the peptide portion and the glycan portion and not through recognition of either the peptide or the glycan alone.

In another embodiment, a panel of the invention comprises a plurality of peptides having an amino acid sequence comprising at least one serine or threonine residue, wherein the residue is a glycosylation site. In yet another embodiment, the at least one serine or threonine residue is at about the middle of the amino acid sequence. In still another embodiment, a panel of the invention comprises mutants of the peptides. The number of peptides in a panel may vary and may be at least 8 peptides, for example between about 8 and about 30 peptides, such as 10, 12, 15 or 20 peptides. A number of peptides in excess of 30 is also within the invention. The upper limit of peptides in a panel is limited by practical considerations (e.g., how many peptides can fit on a substrate) or cost-benefit considerations. Preferably the peptides are selected from the group consisting of SEQ ID NOs 15, 36, 49, and 82-146.

In a specific aspect of the above embodiment, providing a method for identifying glycopeptides reactive with cancer-associated auto-antibodies, the method further comprises identifying cancer-associated glycopeptide epitopes. In another aspect, the method further comprising elucidating the epitope structure of the identified glycopeptide epitopes.

In a specific embodiment, the invention provides a method for determining whether a patient has cancer, the method comprising: contacting an antibody-containing sample from the patient with a panel comprising peptides at least a plurality of which are glycopeptides, each glycopeptide comprising a glycopeptide epitope, the epitope having been previously determined (i) to be selectively recognized by a subset of antibodies in sera from cancer patients, which subset recognizes neither (a) the corresponding naked peptides of the panel when not glycosylated; nor (b) the corresponding glycan when not bound to the peptide; and (ii) not to be recognized by antibodies in control sera; contacting the panel with an antibody-containing sample from the patient; determining if antibodies in the sample are bound to glycopeptides of the panel; and concluding either that the patient has cancer if the sample comprises antibodies that bind to at least one of the glycopeptides in the panel; or that the patient does not have cancer if the sample does not comprise antibodies that bind to at least one glycopeptide in the panel.

In one aspect of the above embodiment providing a method for determining whether a patient has cancer, the patient is newly diagnosed with cancer. In another aspect, the method further comprises concluding either that the patient has cancer if the sample comprises IgG antibodies that bind to at least one of the glycopeptides in the panel; or that the patient does not have cancer if the sample does not comprise IgG antibodies that bind to at least one glycopeptide in the panel. In yet another aspect, the patient is diagnosed with cancer if said sample comprises antibodies that specifically recognize one or more of the glycopeptides having an amino acid sequence selected from the group consisting of: SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQPNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVSDVPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPPSI (SEQ ID NO: 146).

In another embodiment, the invention provides a method for eliciting an immune response in a patient, the method comprising administering to the patient a composition comprising (i) a glycopeptide consisting essentially of an amino acid sequence selected from the group consisting of SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQPNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVSDVPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPPSI (SEQ ID NO: 146), in an effective amount for eliciting the immune response; and (ii) a suitable adjuvant.

In a specific aspect of the above embodiment, providing a method for eliciting an immune response in a patient, the immune response comprises an IgG antibody response. In another aspect, the immune response is an anti-cancer immune response. In yet another aspect, the cancer is selected from the group consisting of breast cancer; colon cancer; ovarian cancer; cervical cancer; pancreatic cancer; prostatic cancer; liver cancer; kidney cancer; brain cancer; hematological cancer; testis cancer; head and neck cancer; and lung cancer.

In one aspect of the above embodiment, providing a method for eliciting an immune response in a patient, the glycopeptide is modified with an O-glycan at at least one amino acid residue. In another aspect, the at least one amino acid residue is a serine or threonine residue.

In any of the above embodiments of the invention, each of the peptides in the panel may be about 2 to about 50 amino acid residues in length. In other aspects, each of the peptides in the panel may be about 4 to about 25 amino acid residues in length.

In certain aspects of the above embodiments of the invention, the amino acid sequence of the peptides of the panel is a fragment found in a protein or variant of said protein or a conservative mutant. In some of the above embodiments, the identified glycopeptides of the panel are found in at least one glycoprotein that is aberrantly glycosylated in cancer cells. In

yet other of the above embodiments, glycopeptides identified by the methods of the present invention are found in at least one glycoprotein that is overexpressed in cancer cells.

In other aspects, the glycopeptides are synthesized synthetically or chemoenzymatically. In still other of the above aspects, the glycopeptides of the panel are partially glycosylated peptides when immobilized on the panel.

In certain of the above embodiments, the control sample contains pooled samples from a plurality of control individuals.

In certain of the above aspects of the invention, the panel is a microarray slide. In other aspects, the glycopeptides identified by the methods of the invention are selectively recognized by an IgG antibody. In certain of the above embodiments, the panel comprises one or more glycopeptides having an amino acid sequence selected from the group consisting of: SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQPNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVSDVPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPPSI (SEQ ID NO: 146).

In another aspect, the invention provides a glycopeptide comprising an amino acid sequence selected from the group consisting of SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQPNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVSDVPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPPSI (SEQ ID NO: 146).

In yet another aspect, the invention provides a glycopeptide consisting essentially of an amino acid sequence selected from the group consisting of SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQPNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVSDVPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPPSI (SEQ ID NO: 146).

In still another aspect, the invention provides a glycopeptide consisting of an amino acid sequence selected from the group consisting of SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49), LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQPNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVSDVPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPPSI (SEQ ID NO: 146).

In another aspect, the invention provides a pharmaceutical composition comprising one or more glycopeptides selected from the group consisting of SEQ ID NOs 15, 36, 49, and 82-146. Preferably, the pharmaceutical composition comprises one or more glycopeptides selected from the group consisting of LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTDPRFQA (SEQ ID NO: 109); PGTSTTPSQPNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVSDVPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPPSI (SEQ ID NO: 146).

In yet another aspect, the invention provides for a panel of glycopeptides comprising at least a plurality of glycopeptides, each glycopeptide comprising a glycopeptide epitope, said epitope having been previously determined (i) to be selectively recognized by a subset of antibodies in sera from cancer patients, which subset recognizes neither (a) the corresponding naked peptides of said panel when not glycosylated; nor (b) the corresponding glycan when not bound to said peptide; and (ii) not to be recognized by antibodies in control sera, said plurality comprising at least 8 glycopeptides selected from the group consisting of glycopeptides having SEQ IDs 15, 36, 49, and 82-146. Preferably, the plurality of glycopeptides comprises SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQPNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVSDVPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPPSI (SEQ ID NO: 146).

In any of the above embodiments of the invention, the glycopeptides of the panel may be glycosylated in situ, in solution, or in vivo by recombinant expression in a host cell. In any of the above embodiments, the glycopeptides of the panel may be treated with one or more exoglycosidases to expose O-glycans. In still other of the above embodiments, the glycan may be an O-glycan. In any of the above embodiments, the O-glycan may be a member selected from the group consisting of: Tn, STn, T, Truncated C3, Truncated C2, Truncated C4, non-capped type1-C3, non-capped type2-C2, non-capped type2-C4, GalNAca-Tn, SA-type1-C3, SLea-C3, LacDiNAc-C3, LacDiNAc-C2, and LacDiNAc-C4.

In certain of the above embodiments, at least one glycopeptide in the panel is not a glycopeptide comprising a glycosylated GSTA motif.

In certain of the above embodiments, none of the glycopeptides in the panel are glycopeptides comprising a glycosylated GSTA motif.

These and other aspects of the present invention will be apparent to those of ordinary skill in the art in light of the present specification, claims and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an image of a microarray slide and illustrates an example of on-slide (in vitro) glycosylation with a polypeptide GalNAc-transferase, GalNAc-T3, to glycosylate peptides and GalNAc glycopeptides with additional unsubstituted Ser/Thr residues to enhance number of O-glycans. FIG. **1**A: GalNAc-T3 untreated array, FIG. **1**B: GalNAc-T3 treated array.

FIG. **2** is an image of a microarray slide and illustrates reactivities of serum (1:25 dilution) from a newly diagnosed prostate cancer patient (#762 in FIG. **2**A) and a normal control serum from an individual that does not have prostate cancer (#174 in FIG. **2**B) on the library of 96 paired peptides/GalNAc-glycopeptides as designated in Table II.

FIGS. **3-5** are bar graphs and illustrate microarray screening results from 147 cancer and 31 control sera on the glycopeptide pairs identified herein as #20/21 (FIG. **3**), #62/63 (FIG. **4**), or #86/87 (FIG. **5**).

FIG. **6** are bar graphs showing 8 selected glycopeptides (i.e., 889, 275a, 585, 893, 931-C3, 852-C3, 873, and 690) reactive with IgG from newly diagnosed cancer patients compared to normal control sera. FIG. **6**A: glycopeptides 889 (SEQ ID NO: 134), 275a (SEQ ID NO: 86), and 585 (SEQ ID NO: 109). FIG. **6**B: glycopeptides 893 (SEQ ID NO: 135), 931-C3 (SEQ ID NO: 146), and 852-C3 (SEQ ID NO: 145). FIG. **6**C: gycopeptides 873 (SEQ ID NO: 132) and 690 (SEQ ID NO: 116). The following human sera were used for FIGS. **6**A and **6**B: 32 ovarian cancer (O), 38 breast cancer (B), 54 colon cancer (C), 17 lung cancer (L), as well as 145 normal sera (N) (Asterand Corp). The following sera were used for FIG. **6**C: 32 ovarian cancer (O), 38 breast cancer (O), 54 colon cancer (C), 42 lung cancer (L), 52 pancreactic cancer (Pn), 35 prostatic cancer (Pr), 8 inflammatory disease (In), 8 benign controls (Bn), and 145 healthy controls (N). Sera were screened at 1:20 dilution. Anti-human-IgG conjugated to Cy3 was used as the secondary detection unit and slides were scanned with a GenePix 4200AL Microarray Scanner.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for identification of peptides and peptide epitopes that comprise one or more posttranslational modification(s) (PTM(s)) ("PTM-peptides"/"PTM peptide epitopes") that are selectively recognized and bound by human disease-associated antibodies. These will include peptides that display an aberrant glycosylation pattern either due to an alteration in sequence (mutation) which invites a changed glycosylation pattern, or simply a glycosylation pattern not normally encountered in cancer-free individuals. Such peptides will constitute AGP as the term is introduced and hence defined above. For the removal of doubt, PTM-epitopes are not whole molecules; therefore, any discussion of such epitopes should be construed as applying to glycopeptides harboring such epitopes.

In some aspects, the PTM-peptides of the invention are useful for diagnosing a disease. In a specific embodiment, the present invention provides methods for diagnosing a patient with cancer. In another embodiment, the patient is newly diagnosed with cancer (i.e., diagnosed with cancer for the first time). In still other embodiments, a patient is diagnosed with an autoimmune disease.

In certain embodiments, the methods are useful for identifying PTM-peptides that are useful for eliciting in an individual an immune response directed against PTM-epitopes that are associated with disease, such as cancer. In certain embodiments, the immune response includes an auto-antibody response. In certain aspects, the induction of auto-antibodies to aberrant PTM-modified glycoproteins includes antibodies that specifically recognize O-glycopeptide epitopes.

As discussed, supra, malignant transformation of cells is virtually always accompanied by alterations in the posttranslational modifications (PTMs) of proteins, including O-glycosylation (Tarp and Clausen 2008). Tumor-associated changes in expression of O-glycoproteins and/or in their aberrant glycosylation, create a diverse set of unusual molecular structures found on the surface of cancer cells as well as in secretions. These molecular structures generally represent glycoproteins with truncated immature O-glycans, to which the immune system of man is not normally exposed except, in some cases, as biosynthetic intermediates and then only in the secretory pathway. Thus, one aspect of the PTM-peptides and PTM peptide epitopes identified by the methods of the present invention, i.e., AGP, is that they are not covered by immunological tolerance, and hence are potential targets for immunotherapeutic intervention. The aim of eliciting immune responses in a host using the AGP of the invention is the development of vaccines against the very disease that the AGP or other PTM-peptides are associated with.

Thus, AGP can cause induction of auto-antibodies to PTM-peptide epitopes. One aspect of this invention is the design and production of PTM-peptide libraries that represent or more accurately contain AGP associated with disease. In another aspect of the invention, high through-put methods for screening of disease-associated antibodies using such libraries are provided. In a specific embodiment, the invention relates to aberrant O-glycosylation of glycoproteins and more specifically, of glycopeptides. The present inventors believe one of the reasons why these disease-associated PTM-peptides and epitopes have eluded detection and especially association with disease is that the proteins bearing them in vivo are not or not necessarily mutated or overexpressed and hence would not be detected by ordinary, nontargeted, techniques.

PTM modifications can be the result of the addition of chemical groups to a protein, such as a phosphate group or a sugar moiety (e.g. acetylation of lysine and serine, glycosylation of asparagine, serine, threonine, hydroxyl-proline, lysine, methylation of arginine, histidine, and lysine, phosphorylation of serine, threonine, and tyrosine). They can also be the result of a conversion of an amino acid to a distinct structure, as in the deimination of arginine to citrulline or the deamidation of aspartic acid/asparagine to isoaspartic acid. While this invention is primarily concerned with glycosylation, it is evident that other aberrant posttranslational modifications as described herein may result in altered proteins harboring aberrant PTM-epitopes that may be the target of auto-immunity.

In some aspects of the present invention, the discriminating characteristic of the peptides and peptide epitopes useful in the present invention is that disease-associated antibodies bind selectively with the PTM-containing peptide and not with the same unmodified peptide or the PTM in the context of a different peptide sequence or another unrelated (e.g., artificial) carrier. In terms of AGP having diagnostic and/or immunogenic value, the disease-associated autoantibodies should recognize only the combination of the relevant glycosylated amino acid sequence and not the same glycan on a different peptide nor the same amino acid sequence bearing a different glycan. This will avoid false positives. It will be understood that the construction of peptide libraries and the availability of disease (e.g., cancer) and control sera that can be tested renders it unnecessary to know beforehand which AGP will be recognized by disease-associated antibodies in order to identify these antibodies. Once the disease-associated antibodies have been identified, they, or man-made versions thereof can be used to pinpoint the AGP that pulled relevant autoantibodies out of the sera.

In other aspects, the invention provides methods for the diagnosis of a patient with a disease, such as, e.g., cancer, wherein detection of antibodies in a sample from the patient that selectively recognize one or more combinations of disease-associated PTM-containing peptides is used to predict

and diagnose disease. In still other embodiments, methods for treating a patient with cancer using compositions or vaccines comprising PTM-containing peptides or proteins of the invention are provided.

DEFINITIONS

As used herein, the term "immune response" includes an adaptive immune response, including a T cell response and B cell response. Thus, as used herein, the term "eliciting an immune response" means that an adaptive immune response is induced by administration of an appropriate immunogen (antigen or antigen plus carrier).

As used herein, an "anti-cancer immune response" is an immune response that is directed toward cancer cells or products secreted or shed from cancer cells. For example, an anti-cancer immune response may be characterized by tumor-specific antibodies and/or cytotoxic T cells that attack cancer cells or react specifically with a glycoprotein shed from cancer cells.

An "auto-antibody" is an antibody that specifically recognizes an epitope harbored by a self-product such as a protein, carbohydrate or lipid produced by healthy or diseased cells of an individual.

As used herein, the terms "selective binding" and "selective recognition" and their grammatical variants, of an epitope by an antibody means that the antibody binds with significantly greater affinity to the epitope compared to any other sequence or structure.

The term "epitope" refers to the part of an antigen that is specifically recognized and bound by an antibody. The term "glycopeptide epitope" is an epitope that includes both part of a peptide sequence and at least part of a glycan. The term "minimal epitope" or "minimal glycopeptide epitope" refers to the shortest glycopeptide that is recognized by antibodies recognizing the same epitope.

As used herein, the term "corresponding peptide" refers to the unglycosylated form of a glycopeptide of the invention. Thus, a glycopeptide and its corresponding peptide have the same amino acid sequence.

The term "glycan hapten" refers to glycan moiety independent of whether this is conjugated to a carrier, such as a peptide or protein (i.e. binding to the glycan hapten does not depend on the carrier such as protein or peptide to which the glycan is bound).

The terms "linear peptide" and "linear peptide epitope" means that the peptide or peptide epitope is non-conformational (i.e., antibody recognition and binding to the epitope does not depend upon the three-dimensional structure of the peptide).

The term "disease-associated antibody" means an antibody that is detected in a patient sample if the patient has the disease, but is not detected, or is present at significantly reduced levels compared to the patient sample, in a control sample. For example, a cancer-associated antibody is present in an antibody-containing sample from a patient with cancer, but is not present, or is present at significantly reduced levels in a sample from a patient without cancer. A useful distinguishing range of antibody levels is at least two or preferably three 3 fold higher levels in patients compared to healthy control. The term may also apply to groups of patients with a disease, where "disease-associated antibody" means an antibody that is detected with higher prevalence/incidence in the disease group compared to a healthy control group. A useful distinguishing prevalence (=specificity of assay) would be at least 70% and preferably 80 or 90%,

The term "aberrant glycosylation" means a glycoform that is not normally present on proteins expressed on the cell surface or secreted/shed from cells. An example of an aberrant glycoform is Tn (GalNAcα1-O-Ser/Thr), sialosyl-Tn (NeuAcα2-8GalNAcα1-O-Ser/Thr), and T (Galβ1-3GalNAcα1-O-Ser/Thr).

As used herein, a "glycosylatable peptide" or a peptide containing a "site amenable to glycosylation" refers to a peptide containing an amino acid residue that can be glycosylated. An example of a site amenable to glycosylation is a peptide site containing a serine or threonine amino acid residue, which can be O-glycosylated with N-acetyl-galactosamine (GalNAc).

As used herein, "variant" in addition to its understood meaning as a term of art includes any changes in a molecule from its wild-type form. For example, alleles, fragments, mutations, substitutions with natural or analog compounds, splice variants, glycosylations, species variants, and the like. The term is not limited to any one type of change or deviation from the wild type form or "normal" molecule. A "variant" also includes a polypeptide or enzyme which has at least 60% amino acid identity as determined by BLAST or FASTA algorithms, preferably at least 75%, most preferably at least 85%, and even more preferably at least 90%, and still more preferably at least 95%, and which has the same or substantially similar properties or functions as the native or parent protein or enzyme to which it is compared.

"Conservative mutants" are those in which a given amino acid residue in a protein or enzyme has been changed without altering the overall conformation and function of the polypeptide, including, but not limited to, replacement of an amino acid with one having similar properties (such as, for example, polarity, hydrogen bonding potential, acidic, basic, hydrophobic, aromatic, and the like). Amino acids with similar properties are well known in the art. For example, arginine, histidine and lysine are hydrophilic-basic amino acids and may be interchangeable. Similarly, isoleucine, a hydrophobic amino acid, may be replaced with leucine, methionine or valine. Such changes are expected to have little or no effect on the apparent molecular weight or isoelectric point of the protein or polypeptide.

An "organ-specific glycoprotein" is a glycoprotein which is only or which has substantial preferential expressed in a specific organ type. For example, the protein mucin 16 (MUC16) (SEQ ID NO: 57), is only expressed in epithelium of the female tract such as ovary and endometrium, and it is primarily overexpressed in tumors originating from these epithelia.

The term "clinical debut" refers to the first time a patient is diagnosed with a disease.

The term "immunogenic substitution" means the replacement of an amino acid residue with a different amino acid that causes the antigen to become immunogenic. For example, a substitution of an amino acid in a self protein, such as that which can result from a cancer mutation, or experimentally in a peptide, that renders the self protein immunogenic (i.e., breaks immunogenic tolerance to the self protein) is an immunogenic substitution. As another example, the substitution of a normally unmodified amino acid with a modified amino acid, wherein the modification itself (i.e., as a hapten, such as, e.g., Tn) is immunogenic, can render a protein immunogenic.

The term "subject" or "individual" as used herein refers to an animal having an immune system, preferably a mammal (e.g., rodent, such as mouse). In particular, the term encompasses humans.

As used herein, the term "about" or "approximately" usually means within an acceptable error range for the type of value and method of measurement. For example, it can mean within 20%, more preferably within 10%, and most preferably still within 5% of a given value or range. Alternatively, especially in biological systems, the term "about" means within about a log (i.e., an order of magnitude) preferably within a factor of two of a given value.

As used herein, the term "consisting essentially of" means that the glycopeptide sequence is not limited to a length of 20 amino acids, but can be longer or shorter. For example, a glycopeptide can be less than or more than 20 amino acids long as established during the course of optimizing the length of the peptide and efficient positioning of the glycosylated epitope that is specifically recognized by auto-antibodies in patients. Throughout the specification, the length of 20 amino acids is used as a convenient length and to ensure that the entire epitope is encompassed within the peptide. While most epitopes will be on the order of 5-10 amino acid residues, and hence contained within a 20 amino acid peptide, any size peptide is possible if sufficient to contain the epitope for antibody detection. In turn, longer peptides may allow for incorporation of additional epitopes which could provide different selectivity for cancer.

Post-Translational Modification of Peptides

In some aspects, the invention relates to the identification of disease-associated PTM-peptides, wherein the PTM-peptide is selectively recognized by disease-associated antibodies. Preferably, the disease-associated antibodies recognize neither the peptide alone nor the PTM alone or attached to a different peptide. In other words, the antibody epitope comprises both part of the protein backbone and part of the PTM.

The PTM may be one or more modifications of one or more residues of the amino acid sequence. The PTM can be any of the known PTMs involving enzymatic modifications of amino acids including glycosylation, phosphorylation, citrinylation, acetylation, methylation (Anderton 2004; Doyle and Mamula 2005; Doyle and Mamula 2001).

All 20 primary amino acids used by man are capable of undergoing some type of PTM. However, certain factors determine whether those modifications will take place. First, the location of the amino acid within the protein sequence affects both the type and frequency of modifications that may arise. Flanking residues can influence the conformation of the protein, potentially altering whether an enzyme has access to a certain amino acid or is exposed to a certain environment. The cellular location of the modifying enzyme, if required, will determine whether the modification occurs and disease-associated changes in localization of such enzymes may lead to aberrant posttranslational modifications. Previous modifications or proteolytic cleavages within a protein influence subsequent amino acid modifications within the same protein.

An exemplary PTM of the invention is mucin-type O-linked glycosylation ("O-glycosylation" or "O-linked glycosylation"). Examples of O-linked glycosylation include, e.g., the addition of N-acetyl-galactosamine (GalNAc), fucose, glucose, N-acetylglucosamine (GlcNAc), or mannose. GalNAc O-glycosylation is a particularly preferred PTM of the invention. GalNAc O-glycosylation is carried out by specific enzymes; for example, the addition of N-acetyl-galactosamine (GalNAc) to serine or threonine residues is carried out by the enzyme UDP-N-acetyl-D-galactosamine: polypeptide N-acetylgalactosaminyltransferase (EC 2.4.1.41). Other types of O-glycosylation include αMannose, αFucose, βGlucose, βGlcNAc, and βXylose glycosylation. Also contemplated by the present invention are other forms of glycosylation, such as, e.g., N-linked glycosylation, hydroxyl-lysine glycosylation, and C-mannosylation. Biosynthesis and structures of these types of protein glycosylation are reviewed in Essentials of Glycobiology (2^{nd} edtion, eds A. Varki, Cummings, Esko, Freeze, Stanley Bertozzi, Hart, Etzler. CSH Press 2009). It is to be understood that examples of PTM modification provided herein, such as O-glycosylation, are meant to be non-limiting examples which serve to prove the principal of the present methods (i.e., that the presently disclosed methods are useful for identifying PTM-modified peptides or peptide epitopes specifically recognized by disease-associated antibodies). The methods of the invention are also applicable, however, to proteins or peptides modified with other PTMs contemplated by the present invention, such as but not limited to phosphorylation, citrinylation, acetylation, and methylation.

In certain aspects of the invention, glycoproteins, glycopeptides and glycopeptide epitopes that are aberrantly glycosylated are provided. Examples of aberrant forms of O-glycans include, but are not limited to, truncated immature O-glycans such as Tn, T, and STn as well as non-sialylated and non-galactosylated core 2, 3 and 4 structures, shown in Table I below:

TABLE I

Representative mucin-type O-glycan structures on normal and diseased cells[1]

Name	Hapten Structure (+/−Ser/Thr or artificial linker)	Type of Glycoconjugate	Distribution (main)	No
Tn	GalNAcα1-O-Ser/Thr	O-linked	Cancer cells	1
STn	NeuAcα2-3GalNAcα1-O-Ser/Thr	O-linked	Cancer cells	2
T	Galβ1-3GalNAcα1-O-Ser/Thr	O-linked	Cancer cells	3
mSTa	NeuAcA2-3Galβ1-3GalNAcα1-O-Ser/Thr	O-linked	Normal cells	4
mSTb	NeuAcA2-3Galβ1-3[NeuAcα2-6]GalNAcα1-O-Ser/Thr	O-linked	Normal cells	5
Truncated C3	GlcNAcβ1-3GalNAcα1-O-Ser/Thr	O-linked	Cancer cells	6
Truncated C2	$(NeuAc2\text{-}3)_{+/-}$_Galβ1-3[GlcNAcβ1-6]GalNAcα1-O-Ser/Thr	O-linked	Cancer cells	7
Truncated C4	GlcNAcβ1-3[GlcNAcβ1-6]GalNAcα1-O-Ser/Thr	O-linked	Cancer cells	8
Non-capped type1-C3	Galβ1-3G1cNAcβ1-3GalNAcα1-O-Ser/Thr	O-linked	Cancer cells	9
Non-capped type2-C2	$(NeuAc2\text{-}3)_{+/-}$_Galβ1-3[Galβ1-4GlcNAcβ1-6]GalNAcα1-O-Ser/Thr	O-linked	Cancer cells	10
Non-capped type2-C4	(Galβ1-4)GlcNAcβ1-3[Galβ1-4GlcNAcβ1-6]GalNAcα1-O-Ser/Thr	O-linked	Cancer cells	11
GalNAca-Tn	GalNAcα1-3GalNAcα1-O-Ser/Thr	O-linked	Cancer cells	12

TABLE I-continued

Representative mucin-type O-glycan structures on normal and diseased cells[1]

Name	Hapten Structure (+/−Ser/Thr or artificial linker)	Type of Glycoconjugate	Distribution (main)	No
SA-type1-C3	NeuAcα2-3Galβ1-3GlcNAcβ1-3GalNAcα1-O-Ser/Thr	O-linked	Cancer cells	13
SLe^a-C3	NeuAcα2-3Galβ1-3[Fucα1-4]GlcNAcβ1-3GalNAcαl-O-Ser/Thr	O-linked	Cancer cells	14
LacDiNAc-C3	GalNAcβ1-3/4G1cNAcβ1-3GalNAcα1-O-Ser/Thr	O-linked	unknown	15
LacDiNAc-C2	Galβ1-3[GalNAcβ1-3/4G1cNAcβ1-6]GalNAcα1-O-Ser/Thr	O-linked	unknown	16
LacDiNAc-C4	GalNAcβ1-3/4GlcNAcβ1-3[GalNAcβ1-3/4GlcNAcβ1-6]GalNAcα1-O-Ser/Thr	O-linked	unknown	17

[1]Additional modifications such as capping terminal β3/4Gal residues with Fucαl -2 (blood group H) and Gal(NAc)α1-3 (blood group A,B) are generally produced by normal cells. Modifications such as 3/6-O-SO_3 of Gal and GalNAc, 9-O-acetylation of NeuAc, NeuGc instead of NeuAc, may also occur in normal and cancer cells.

In some aspects of the invention, the glycopeptide sequences of the invention may be derived from disease-associated proteins, such as, e.g., a glycoprotein specifically expressed on the cell surface of a cancer cell, but not on the surface of a non-malignant cell, or overexpressed on cancer cell surfaces, e.g., mucin 1 (MUC1) (GenBank Accession Nos. NP__002447 (SEQ ID NO: 1); NP__001018016 SEQ ID NO: 2); NP__001018017 (SEQ ID NO: 3); NP__001037855 (SEQ ID NO: 54); NP__001037856 (SEQ ID NO: 55); and NP__001037857 (SEQ ID NO: 56)); MUC16 (GenBank Accession No. NP__078966 (SEQ ID NO: 57); and mesothelin (MSLN) (GenBank Accession Nos. NP__037536 (SEQ ID NO: 58) and NP__005814 (SEQ ID NO: 59). In some embodiments, the glycoproteins are organ-specific glycoproteins. Examples of such glycoproteins include MUC16 (expressed in the female reproductive tract) and mesothelin, which is specifically expressed in the normal lung, but with cancer expression in ovarian and cervical cancers. Specific examples of other glycoproteins of the invention include, but are not limited to, human proteins predicted from the completed human genome containing one or more serine and/or threonine GalNAc O-glycosylation sites as predicted by the NetOGlyc algorithm.

Non-limiting examples of such proteins include cell membrane receptors such as low-density lipoprotein receptor precursor (LDLR) (GenBank Accesion No. NP__000518) (SEQ ID NO: 67)), very low-density lipoprotein receptor precursor (VLDLR) (GenBank Accession Nos. NP__001018066 (SEQ ID NO: 68) and NP__003374 (SEQ ID NO: 69)), and receptor tyrosine-protein kinase erbB-2 precursor (ERBB2) (GenBank Accession Nos. NP__004439 (SEQ ID NO: 70) and NP__001005862 (SEQ ID NO: 71)); chaperones such as heat shock 70 kDa protein 5 (HSPA5) (GenBank Accession No. NP__005338 (SEQ ID NO: 72) and heat shock 70 kDa protein 8 (HSPA8) (GenBank Accession No. NP__694881) (SEQ ID NO: 73) and NP__006588 (SEQ ID NO: 74); secreted cytokines, growth factors and glycoproteins such as interferon alpha-2 precursor (IFNA2) (GenBank Accession No. NP__000596) (SEQ ID NO: 75), interleukin-2 (IL2) (GenBank Accession No. NP__000577) (SEQ ID NO: 76), and inhibin beta B chain precursor (INHBB) (GenBank Accession No. NP__002184) (SEQ ID NO: 77); proteases such as matrix metalloproteinase-14 precursor (MMP14) (GenBank Accession No. NP__004986) (SEQ ID NO: 78); enzymes such as prostatic acid phosphatase precursor (ACPP) (GenBank Accession Noa. NP__001127666) (SEQ ID NO: 79) and NP__001090 (SEQ ID NO: 80); and mucins such as melanoma cell adhesion molecule (MCAM) (GenBank Accession No. NP__006491) (SEQ ID NO: 81).

In other embodiments, glycopeptide mutants are contemplated for use in the present invention. For example, a peptide library can be generated wherein each amino acid in the peptide sequence around one or more sites for PTM modification (e.g., O-glycosylation) is varied by any combination of the 20 amino acids used in human proteins to form additional peptide sequences (i.e. mutants) with the same PTM motif.

In certain embodiments, the present invention further relates to the design of glycopeptide libraries for screening disease-associated antibodies and/or for identifying disease-associated glycopeptides and/or glycopeptide epitopes. In certain aspects, a glycopeptide library of the invention is provided as a glycopeptide panel for identifying glycopeptides reactive with disease-associated auto-antibodies. A "glycopeptide panel" comprises at least two glycopeptides (or indeed entire glycoproteins) and may be used in an antibody binding assay of the invention. In certain aspects, methods for designing both the sequence of the glycopeptide and the specific site(s) for glycosylation are provided.

Preferably, glycopeptides of the glycopeptide libraries of the invention are from about 4 to about 50 amino acids in length. More preferably, such glycopeptides are from about 4 to about 25 amino acid residues in length.

In certain aspects, peptides are designed as fragments of a glycoprotein. A random peptide library encompassing peptides having between about 4 and about 50 amino acids, is provided, wherein each amino acid in each peptide is varied by all 20 amino acids used in human proteins to form different peptide sequences. These random peptides are PTM-modified, e.g., O-glycosylated, on at least one amino acid residue. In other aspects, the peptide library comprises peptides covering all serine and threonine residues in the predicted human protein sequences. In yet another aspect, peptides of the glycopeptide libraries comprise sequences derived from disease-associated proteins and/or organ-specific proteins, as described, supra.

In certain embodiments of the invention, a peptide suitable for testing is a potential acceptor of GalNAc O-glycosylation by polypeptide GalNAc-transferases if: 1) the peptide is a sequence derived from the human proteome, wherein the human proteome may be predicted from the human genome; and 2) the peptide comprises one or more serine and/or threonine residues. Preferably, such peptides are derived from proteins that have a signal sequence. It is also preferred that such peptides have sequences that, in vitro, serve as substrates for one or more human polypeptide GalNAc-transferases, such as, e.g., GalNAc-T1, T2, T3, or T4. The initiating enzymes for other types of O-glycosylation that attaches the first sugar residue to Serine and Threonine residues of

polypeptides have been cloned and expressed recombinantly and hence these types of modifications are amiable to the same strategy for testing (Essentials of Glycobiology (2^{nd} edtion, eds A. Varki, Cummings, Esko, Freeze, Stanley Bertozzi, Hart, Etzler. CSH Press 2009).

In certain aspects, it is preferred that the glycopeptides of the invention comprise sequences predicted by the NetOGlyc algorithm. The NetOGlyc algorithm has been developed to predict sites and proteins modified by O-glycosylation and this has been postulated to have a positive prediction rate of 76% (Julenius et al. 2005).

In other embodiments, peptides may be modified with other PTM modifications.

Glycopeptide Synthesis

In some aspects of the invention, the peptide sequence of the glycopeptides of the invention can be synthesized using standard chemical synthesis [Meldal M, Bock K. A general approach to the synthesis of O- and N-linked glycopeptides. Glycoconj J. 1994; 11(2):59-63]. For example, GalNAcα-Ser/Thr-Fmoc, GlcNAcα-Ser/Thr-Fmoc, Manα-Ser/Thr, and Glcβ-Ser/Thr amino acids are commercially available (Sussex Inc (Canada)), and may be incorporated into the peptides during synthesis. The glycopeptides of the invention may be synthesized with and without an N-terminal linker for printing on epoxy or NHS-activated glass slides, respectively. In certain embodiments, glycopeptides may also be synthesized directly on microarray slides ("spot synthesis"). In other embodiments, peptides are previously synthesized and then immobilized or used in solution, according to a method of the present invention.

In certain aspects, the synthesized peptides or glycopeptides are O-glycosylated or further O-glycosylated using enzymatic synthesis of O-glycans at specific sites to form glycopeptides (Tarp and Clausen 2008).

In certain aspects of the present invention, the peptides may be glycosylated by a number of different methods, such as e.g., on-slide glycosylation, in solution glycosylation, or in vivo, e.g., by recombinant expression in appropriate host cells (Tarp et al. Glycobiology 2007).

Glycosylation may be achieved using one or more recombinant glycosyltransferases. such as, e.g., recombinant polypeptide GalNAc-transferases (e.g. GalNAc-T2, -T3 and -T4). See, e.g., U.S. Pat. No. 5,876,716 by Hansen and U.S. Pat. No. 6,465,220 by Hassan; see also, Bennett et al. 1998; Bennett et al. 1996; and White et al. 1995.

Further expansion may also be achieved using a recombinant sialyltransferase, ST6GalNAc-II, to produce STn glycoforms (structure no. 2, Table I) of the GalNAc glycopeptides. T glycoforms may be produced by a recombinant *Drosophila* core1 β3galactosyltransferase, truncated core3 glycoforms (structure no. 6, Table I) may be produced using a recombinant human β3GlcNAc-transferase (Iwai et al. 2002), and non-capped type1-core3 glycoforms (structure no. 9, Table I) may be produced using β3Gal-T5 (see, U.S. Pat. No. 7,332,279).

In other aspects, the glycopeptides and/or glycoproteins of the invention may be derived from recombinant or isolated glycopeptides or glycoproteins and further glycosylated or modified according to the methods of the present invention. For example, commercially available glycoprotein arrays (available, e.g., from Invitrogen), may be treated with exoglycosidases, e.g., neuraminidase, βgalactosidase, βN-acetylglucosaminidase and other enzymes, in order to expose cancer-associated glycans, e.g., Tn or T, to form glycopeptides according to the present invention.

In certain aspects of the invention, the O-glycan is preferably positioned in the center of the peptide. While not intending to be bound by a specific theory, positioning the O-glycan in the center of the peptide may facilitate proper presentation of the O-glycan for specific antibody binding to a glycopeptides epitope. In certain aspects, for example, in a glycopeptide of 20 amino acid residues in length, the O-glycan is preferably attached to a serine or threonine amino acid residue placed at a site from about residue 6 to about residue 15 and more preferably from about residue 8 to about residue 13. For example, in the present Examples, glycopeptides were designed with a single GalNAc at position 12 (of the 20-mer) to allow optimal exposure of peptide sequence flanking the O-glycan, taking into consideration that the glycopeptides will be covalently linked primarily through the N-terminal amino acid.

In certain aspects, the O-glycans to be presented on a glycopeptide library of the invention may include all known O-glycan structures. In preferred embodiments, the glycopeptides comprise glycans known to be disease-associated, such as Tn, STn, T, Truncated C3, Truncated C2, Truncated C4, non-capped type1-C3, non-capped type2-C2, non-capped type2-C4, GalNAcα-Tn, SA-type1-C3, SLea-C3, LacDiNAc-C3, LacDiNAc-C2, and LacDiNAc-C4 (see Table I for additional non-limiting examples of such glycans). Further the O-glycans may be substituted with sulfation or other immunogenic substitutions including acetylation and artificial chemical groups.

Screening Assays

In certain embodiments, the present invention provides methods for identifying glycopeptides and/or glycopeptide epitopes reactive with disease-associated auto-antibodies using an assay comprising one or more glycopeptide panels. Preferably, such auto-antibodies bind glycopeptide epitopes through recognition of both the peptide portion and the glycan portion, but not through recognition of either the peptide or the glycan alone. The panel is contacted with a sample containing the disease-associated antibodies (e.g., sera obtained from an individual with the disease).

In a specific embodiment, the invention provides a method for identifying glycopeptides reactive with cancer-associated auto-antibodies, wherein the method comprises: (a) providing a panel comprising glycopeptides having a peptide portion and a glycan portion; (b) contacting the panel with an antibody-containing a sample from a patient with cancer; and (c) identifying glycopeptides in the panel that (i) are selectively recognized by antibodies in the sample, but not by antibodies in a control sample, and (ii) are recognized by such antibodies in the sample through recognition of both the peptide portion and the glycan portion, but not through recognition of either the peptide or the glycan alone.

Non-limiting examples of suitable antibody-containing samples for the assays of the present invention include serum, plasma, body fluids such as milk, saliva, mucosal secretions, feces, urine, cells and tissues, and any antibody preparations thereof.

Further, in order to develop the glycopeptide screening assays of the present invention, a control sample is used. By "control sample", it is meant a sample containing pooled sera obtained from apparently disease-free or healthy individuals (i.e., individuals who do not have the disease-associated antibodies in their serum because they do not have the relevant disease), or, it is meant multiple control samples, wherein each sample is obtained from a single apparently healthy (disease-free) individual, and then data obtained in the assay for the tested control samples are compared in order to exclude any samples from control individuals who are sus-

pected to in fact not be healthy, based on the presence of auto-antibodies not present in a statistically significant fraction of the control population.

In certain aspects, the present invention provides methods for identifying cancer-associated glycopeptide epitopes, wherein the epitope includes both part of the glycan of the glycopeptide and part of the peptide amino acid sequence. Such methods can comprise the following steps: (a) providing a panel comprising glycopeptides having a peptide portion and a glycan portion; wherein the peptide amino acid sequences of the glycopeptides are serially shifted 1-5 residues in either direction, to provide a series of overlapping peptide sequences; (b) contacting the panel with an antibody-containing sample from a patient with cancer; (c) identifying glycopeptides in the panel that (i) are selectively recognized by antibodies in the sample, but not by antibodies in a control sample, and (ii) are recognized by such antibodies in the sample through recognition of both the peptide portion and the glycan portion, but not through recognition of either the peptide or the glycan alone; and (d) mapping the minimal glycopeptide epitope based on the pattern of antibody binding to the overlapping glycopeptide sequences.

"Epitope mapping" may be carried out as follows: A glycopeptide epitope comprising e.g., a 20-mer glycopeptide with a single glycan attached to position 12 can be "mapped" in terms of peptide sequence requirement by synthesis of a panel of 20-mer glycopeptides in which each amino acid around the glycan site is modified one by one to an amino acid different from the one present in the identified glycopeptide, e.g. alanine or valine. Analysis of antibody binding to this panel of "walking" alanine or valine residues through the peptide sequence will demonstrate which residues abrogate binding, and thus provide information of the necessary peptide sequence backbone around the glycosylation site required for antibody binding.

In certain aspects of the invention, the minimum glycopeptide epitope is preferably about 2 to about 7 amino acid residues in length, but can extend to up to about 15 residues, and comprises a portion of an O-glycan modifying the glycopeptide epitope. In certain embodiments, the minimal glycopeptide epitope spans about 3 to about 4, about 2 to about 3, or about 1 to about 2 amino acid residues on each side of the O-glycan that is part of the minimal epitope identified by the methods of the present invention. In other embodiments, a greater number of amino acids may be present on one side of the O-glycan compared to the number of amino acids of the minimal epitope on the other side of the O-glycan. The minimum glycopeptide epitope can be, for example, a "minimum cancer-associated glycopeptide epitope," which is the minimum glycopeptide epitope identified by the methods of the present invention to be specifically recognized by a cancer-associated auto-antibody.

In certain embodiments, the epitope structure of the glycopeptide epitopes identified by the present methods is determined by mass spectrometry.

In some aspects, determining whether glycopeptides and/or glycopeptide epitopes are selectively recognized by antibodies in a sample through recognition of both the peptide portion and the glycan portion, wherein the antibodies do not recognize either portion alone, may be achieved as follows: an additional panel may be provided, in which the unglycosylated forms of the glycopeptides are provided (i.e., the corresponding peptides) and antibody binding is determined. In order for a glycopeptide to be selectively recognized by an antibody in the sample, antibody binding to the corresponding peptide should be partially or preferably completely abrogated. Preferably, antibody binding to the corresponding peptide is diminished by at least about 40%, preferably at least about 50%, more preferably at least about 60%, even more preferably at least about 70%, still more preferably at least about 80%, more preferably at least about 85%, still more preferably at least about 90%, and most preferably 95% to 100% compared to antibody binding to the glycopeptide.

In other aspects of the present invention, methods of determining the presence of auto-antibodies binding O-glycopeptides, may also comprise the step of contacting the panel with a peptide inhibitor in order to exclude antibodies that recognize the non-glycosylated form of the glycopeptide. Peptide inhibitors are typically a peptide of the same amino acid sequence as the glycopeptide, however, without any glycosylations.

In other embodiments, antibodies that recognize only the hapten glycan or the glycan-conjugated to a different peptide or artificial carrier may be excluded, in order to prevent identification of epitopes that consist only of the glycan hapten. This can be achieved in several ways. For example, in certain embodiments, hapten-specific antibodies may be removed from the sample prior to analysis.

In some embodiments, hapten-specific antibodies may be removed by affinity chromatography with an appropriate resin with covalently linked carbohydrate haptens, or by inhibition with carbohydrate haptens in solution during binding assays. An example of preferable resin is GalNAc-Sepharose or other appropriate resins that would be able to bind anti-Tn hapten antibodies. Other preferable resins are GlcNAc-Sepharose, Man-Sepharose, Glc-Sepharose or Fuc-Sepharose and without limitations corresponding di- and trisaccharides in the biosynthetic pathways bound resins.

In other embodiments, hapten-specific antibodies may excluded from binding to glycopeptides in the binding assays of the present invention using a carbohydrate inhibitor. In some embodiments, the carbohydrate inhibitor comprises a normal occurring O-glycan such as sialylated or fucosylated core 2, 3, or 4 O-glycan, as is typically present in normal cells. In some aspects, the carbohydrate inhibitor may be Tn, STn, T or other truncated O-glycan structures based on core 3 or 4. Also preferred are polyvalent PAA (polyacrylamide) conjugates (GlycoTech, US) of the aforementioned carbohydrates. Still in another embodiment, the carbohydrate inhibitor is a monosaccharide such as GalNAc, GlcNAc, Gal, Glc, Fuc, Man, Xyl and NeuAc. It will be apparent to the skilled artisan that other combinations of carbohydrates will have the same effect.

The above-described methods, as well as other methods that may be readily determined by a skilled artisan and used to achieve the same effect, may be used to exclude antibodies in a sample that do not specifically recognize the glycopeptide (i.e., through both the peptide and the glycan). In certain embodiments of the invention, exclusion of such antibodies from the analysis is necessary in order to identify the glycopeptides and glycopeptide epitopes that are specifically recognized by disease-associated antibodies.

In certain embodiments, a peptide inhibitor and/or an O-glycan inhibitor may be immobilized on a solid support, which is used to remove antibodies that interact with the peptide inhibitor and/or with the O-glycan carbohydrate inhibitor from a sample, prior to use of the sample according to a method of the present invention.

In some aspects, the screening assays of the present invention involve immobilized glycopeptides; however, in solution assays such as polarization, inhibition and competitive binding assays are also contemplated for use in the present invention. [See, e.g., Smith D S, Eremin S A. Fluorescence polarization immunoassays and related methods for simple, high-

throughput screening of small molecules. Anal Bioanal Chem. 2008; 391(5):1499-507.]

Non-limiting examples of screening assays involving immobilized glycopeptides contemplated for use in the present invention include antibody-binding assays, such as enzyme-linked immunosorbent assay (ELISA), multiplex bead arrays (see, Elshal et al., (2006) Methods; 38(4):317-323); BiaCore SPR analysis where binding affinities can be evaluated and microarray platforms.

In a preferred embodiment, glycopeptide libraries of the invention are immobilized on microarray slides. The glycopeptides may be printed on microarray slides, such as, e.g., Corning, Scineion or Nexterion® Slide H or Schott Nexterion® Slide H MPX 16 (Schott AG, Mainz, Germany) by JPT (Germany). Printing may be carried out using MicroGrid, ArrayIT or similar according to the methods described in (Blixt O, Head S, Mondala T, Scanlan C, Huflejt M E, Alvarez R, Bryan M C, Fazio F, Calarese D, Stevens J, Razi N, Stevens D J, Skehel J J, van Die I, Burton D R, Wilson I A, Cummings R, Bovin N, Wong C H, Paulson J C. Printed covalent glycan array for ligand profiling of diverse glycan binding proteins. Proc Natl Acad Sci USA. 2004; 101(49):17033-8)

Microarray slides of the invention may also be prepared by companies such as Schott (Louisville, Ky.), ArrayIt Corp. (Sunnyvale, Calif.), or Scineon (Germany).

In certain embodiments, assays for large scale screening include, e.g., multiplex bead or array formats where many targets can be assayed simultaneously with very little consumption of antibody. For example, a small volume (50 μl) of an antibody-containing sample (e.g. serum or diluted serum) may be incubated with a solution of beads, wherein each bead is coated with a specific glycopeptide, and each bead possesses a distinguishing characteristic (e.g., size) that allows it to be differentiated from other beads in the sample. If an antibody is present in the sample that recognizes a glycopeptide on one of the beads, it will bind to the bead. Then, specific binding of antibodies to each glycopeptide in the sample may be detected using a detecting reagent, such as, e.g., biotinylated anti-Ig antibody followed by fluorescently-labeled streptavidin. The concentration of antibody in the sample that is specific for each glycopeptide on the bead may then be quantified using a bead analyzer, such as, e.g., the Luminex® 200™ System (Invitrogen).

In yet another embodiment of the invention, the detection of auto-antibodies can be limited to distinct human Ig isotypes and subclasses. Most human natural carbohydrate antibodies are of IgM isotype and it is the detection of auto-antibodies of IgG isotype and subclasses is preferred. More specifically, detection of binding of human IgG antibodies, or IgG1, 2, 3, and 4 individually, with appropriate anti-human antibodies avoid most reactivity with truncated O-glycan haptens such as Tn, STn, T core3, and other truncated structures to which IgM antibodies are found in control samples.

Methods of Diagnosing

In some aspects, the present invention provides methods for diagnosing a patient with a disease. For example, disease-associated glycopeptides and glycopeptide epitopes identified by the methods of the present invention may be used for detection of disease-associated auto-antibodies with the purpose of determining diagnosis and/or prognosis.

For example, in certain embodiments, a patient may be diagnosed as having cancer or as not having cancer, based on the presence or absence, respectively, of specific, cancer-associated glycopeptide-reactive auto-antibodies. In a specific embodiment, the method comprises contacting an antibody-containing sample from a patient with a panel comprising peptides, wherein at least a plurality of the peptides are glycopeptides. Further, each glycopeptide comprises a glycopeptide epitope that has been previously determined (i) to be selectively recognized by a subset of antibodies in sera from cancer patients, which subset recognizes neither (a) the corresponding naked peptides of said panel when not glycosylated; nor (b) the corresponding glycan when not bound to said peptide; and (ii) not to be recognized by antibodies in control sera. It is then determined if antibodies in the sample are bound to glycopeptides of said panel; and concluded either that the patient has cancer if the sample comprises antibodies that bind to at least one of the glycopeptides in the panel; or that the patient does not have cancer if the sample does not comprise antibodies that bind to at least one glycopeptide in the panel.

In certain aspects, the specific type of cancer that may be diagnosed or treated by a method of the present invention without limitation may be selected from the group consisting of breast cancer, colon cancer, ovarian cancer, cervical cancer, pancreatic cancer, prostatic cancer, liver cancer, kidney cancer, brain cancer, hematological cancers, testis cancer, head and neck cancers, and lung cancer.

In yet another embodiment, the diagnostic panel comprises glycopeptides comprising one or more and preferably at least 8 of the amino acid sequences selected from the group consisting of SEQ ID NOs. 15, 36, 49, and 82-146.

In yet another specific embodiment, the diagnostic panel comprises glycopeptides comprising one or more of the amino acid sequences selected from the group consisting of SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQPNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVSDVPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPPSI (SEQ ID NO: 146). Furthermore, these glycopeptides may be O-glycosylated at one or more sites according to the methods of the present invention.

In yet another embodiment, the diagnostic panel comprises at least 8 glycopeptides, for example between about 8 and about 30 glycopeptides, such as 10, 12, 15, or 20 glycopeptides. A number of glycopeptides in excess of 30 is also within the invention. The upper limit of glycopeptides in a panel is limited by practical considerations (e.g., how many glycopeptides can fit on a substrate) or cost-benefit considerations. Preferably the glycopeptides are selected from the group consisting of SEQ ID NOs 15, 36, 49, and 82-146.

In yet other aspects, a patient may be diagnosed as having an autoimmune disease. In certain embodiments, the autoimmune disease is selected from the group consisting of coeliac disease, type I diabetes, multiple sclerosis, thyroiditis, Grave's disease, systemic lupus erythematosus, scleroderma, psoriasis, rheumatoid arthritis, alopecia greata, ankylosing spondylitis, Churg-Strauss Syndrome, autoimmune hemolytic anemia, autoimmune hepatitis, Behcet's disease, Crohn's disease, dermatomyositis, glomerulonephritis, Guillain-Barre syndrome, inflammatory bowel disease (IBD), lupus nephritis, myasthenia gravis, myocarditis, pemphigus/pemphigoid, pernicious anemia, polyarteritis nodosa, polymyositis, primary biliary cirrhosis, rheumatic fever, sarcoidosis, Sjogren's syndrome, ulcerative colitis, uveitis, vitiligo, and Wegener's granulomatosis.

Thus, in some embodiments, a diagnostic panel of the invention comprises glycopeptide epitopes determined by the

methods of the present invention to be associated with an autoimmune disease. For example, in certain embodiments, a patient may be diagnosed as having an autoimmune disease or as not having an autoimmune disease, based on the presence or absence, respectively, of specific, autoimmune disease-associated glycopeptide-reactive auto-antibodies. In a specific embodiment, the method comprises contacting an antibody-containing sample from a patient with a panel comprising peptides, wherein at least a plurality of the peptides are glycopeptides. Further, each glycopeptide comprises a glycopeptide epitope that has been previously determined (i) to be selectively recognized by a subset of antibodies in sera from patients with a specific autoimmune disease, which subset recognizes neither (a) the corresponding naked peptides of said panel when not glycosylated; nor (b) the corresponding glycan when not bound to said peptide; and (ii) not to be recognized by antibodies in control sera. It is then determined if antibodies in the sample are bound to glycopeptides of said panel; and concluded either that the patient has the autoimmune disease if the sample comprises antibodies that bind to at least one of the glycopeptides in the panel; or that the patient does not have the autoimmune disease if the sample does not comprise antibodies that bind to at least one glycopeptide in the panel.

Preparation of Antibodies

Other aspects of the present invention are antibodies prepared using one or more glycopeptides identified using the methods of the present invention, methods for preparation of these antibodies, and the use of such antibodies in therapy and diagnosis.

Yet another aspect of the present invention is a method for the preparation of hybridoma cells, which secrete monoclonal antibodies specific for the glycopeptides of the invention. One such method involves immunizing a suitable mammal with a glycopeptide of the invention; fusing antibody-producing cells of the mammal with cells of a continuous cell line; the hybrid cells obtained in the fusion are cloned; and cell clones secreting the desired antibodies are selected.

Still another aspect is a monoclonal antibody selected from the group consisting of: a monoclonal antibody produced by the hybridoma cells prepared by the method described above; and a monoclonal antibody prepared by molecular display techniques, such as mRNA display, ribosome display, phage display and covalent display against a glycopeptide of the invention.

For preparation of monoclonal antibodies, any technique that provides for the production of antibody molecules by continuous cell lines in culture may be used. These include but are not limited to the hybridoma technique originally developed by Kohler and Milstein (Nature, 1975; 256:495-497), as well as the trioma technique, the human B-cell hybridoma technique (Kozbor et al., Immunology Today, 1983; 4:72, Cote et al., Proc. Natl. Acad. Sci. U.S.A., 1983; 80:2026-2030), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole et al., in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., pp. 77-96, 1985). In an additional embodiment of the invention, monoclonal antibodies can be produced in germ-free animals (International Patent Publication No. WO 89/12690, published 28 Dec., 1989).

According to the invention, techniques described for the production of single chain antibodies (U.S. Pat. Nos. 5,476,786 and 5,132,405 to Huston; U.S. Pat. No. 4,946,778) can be adapted to produce glycopeptide-specific single chain antibodies. Indeed, these genes can be delivered for expression in vivo to, e.g., express a glycopeptide-specific antibody. An additional embodiment of the invention utilizes the techniques described for the construction of Fab expression libraries (Huse et al., Science, 1989; 246:1275-1281) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity for a glycopeptide or glycopeptide epitope of the invention.

Antibody fragments which contain the idiotype of the antibody molecule can be generated by known techniques. For example, such fragments include but are not limited to: the F(ab')2 fragment which can be produced by pepsin digestion of the antibody molecule; the Fab' fragments which can be generated by reducing the disulfide bridges of the F(ab')2 fragment, and the Fab fragments which can be generated by treating the antibody molecule with papain and a reducing agent.

In the production of antibodies, screening for the desired antibody can be accomplished by techniques known in the art, e.g., radioimmunoassay, ELISA (enzyme-linked immunosorbant assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitin reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), Western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

In other embodiments, alternative techniques such as mRNA display, ribosome display, phage display and covalent display may also be used. These are all display techniques where a peptide library is selected against the glycopeptide. Such techniques can e.g. be used to identify humanized or fully human antibodies.

In a preferred embodiment, the monoclonal antibody binds an O-glycoprotein containing the O-glycopeptide epitope on cancer cells but not on a non-malignant counterpart.

In another preferred embodiment, the monoclonal antibody binds preferentially to the O-glycoprotein that is aberrantly glycosylated and expressed on cancer cells.

In still another embodiment, the monoclonal antibody binds to or at least interacts directly with the O-glycopeptide.

In a preferred embodiment, the antibody prepared using a glycopeptide of the invention is humanized or fully human, such as to decrease the immunogenicity of the antibody in humans. This is typically desirable if the antibody is used as a therapeutic. However, in some situations a rapid clearance may be desired, wherefore non-humanized antibodies are also of interest as therapeutics. One such situation can, e.g., be when administering antibody conjugates where antibodies are coupled to toxins or radioisotopes. Such conjugated antibodies should either find their target rapidly or be cleared as they have a general toxic effect. Thus, one embodiment of the invention is conjugated antibodies. Non-limiting examples of antibody conjugates include radioisotopes, such as ^{131}I, ^{90}Y, ^{177}Leutitium (^{177}Lu) and ^{67}Copper (^{67}Cu); toxins, such as the fungal toxin maytansanoid (DM-1); and antibiotics, such as e.g., calicheamicin [See, Ross et al. Antibody-based therapeutics: Focus on prostate cancer. Cancer and Metastasis Reviews 24: 521-537, 2005].

Compositions and Uses

In certain embodiments, the present invention provides compositions comprising one or more disease-associated

glycopeptides and/or glycopeptide epitopes identified by the methods of the present invention. In certain aspects, such disease-associated glycopeptides comprise epitopes specifically recognized and bound by disease-associated antibodies.

In a specific embodiment, a composition of the invention comprises one or more of a glycoprotein or glycopeptide comprising an amino acid sequence selected from the group consisting of SEQ IDs 15, 36, 49, and 82-146. Preferably, the composition comprises one or more of a glycoprotein or glycopeptides comprising an amino acid sequence selected from the group consisting of SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQPNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVSDVPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPPSI (SEQ ID NO: 146). In certain embodiments, such glycoproteins or glycopeptides are further modified at at least one amino acid residue, with an O-glycan. Preferably, the amino acid residue is serine or threonine residue.

In some aspects, the invention provides methods for eliciting an immune response in an individual, wherein the immune responses is specific for one or more glycopeptides or glycoproteins identified by the methods of the present invention.

One aspect of the invention is a method of treating cancer or an autoimmune disease comprising administering a pharmaceutical composition of the invention. In a specific embodiment, a cancer patient is treated by eliciting an anticancer immune response that attacks cancer cells (e.g., tumors). In any of the aspects of the invention, the immune response elicited by a pharmaceutical composition of the invention may be an adaptive T and/or B cell response (e.g., either a cytotoxic T cell response or an antibody response, or both) directed against the cancer cells, which results in reduction or elimination of the cancer cells.

"Treating" or "treatment" of a state, disorder or condition includes: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a human or other mammal that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, i.e., arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

The benefit to an individual to be treated is either statistically significant or at least perceptible to the patient or to the physician.

Pharmaceutical Compositions and Administration

While it is possible to use a composition provided by the present invention for therapy as is, it may be preferable to administer it in a pharmaceutical formulation, e.g., in admixture with a suitable pharmaceutical excipient, diluent, or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Accordingly, in one aspect, the present invention provides a pharmaceutical composition or formulation comprising at least one composition of the invention, or a pharmaceutically acceptable derivative thereof, in association with a pharmaceutically acceptable excipient, diluent, and/or carrier. The excipient, diluent and/or carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compositions of the invention can be formulated for administration in any convenient way for use in human or veterinary medicine.

Pharmaceutical Carrier

The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or aqueous solution saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Alternatively, the carrier can be a solid dosage form carrier, including but not limited to one or more of a binder (for compressed pills), a glidant, an encapsulating agent, a flavorant, and a colorant. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin (1990, Mack Publishing Co., Easton, Pa. 18042).

Vaccines

In certain aspects, a disease-associated glycopeptide or glycoprotein of the present invention is provided in a vaccine. Thus, in certain aspects, such a disease-associated glycopeptide or glycoprotein is provided as an "immunogen" for inducing an immune response. In some aspects, a vaccine of the present invention is useful for treating cancer by inducing an "anti-cancer immune response." Preferably, a vaccine of the present invention in effective for inducing an adaptive immune response that selectively target cancer cells and has minimal reactivity with normal cells.

In certain embodiments, the glycopeptide epitopes identified by the methods of the present invention are targets for spontaneously-induced human auto-antibodies. Thus, it is evident that these epitopes are not generally covered by immunological tolerance. Accordingly, in certain aspects of the invention, a vaccine comprising a glycopeptide immunogen identified by the present methods does not require an adjuvant.

In other embodiments, a vaccine comprising a glycopeptide immunogen of the invention may additionally contain adjuvants to induce or enhance the desired immune response, such as, e.g., an anti-cancer immune response. Exemplary adjuvants include, but are not limited to, cholera toxin, fragments and mutants or derivatives with adjuvant properties, *E. coli* heat-labile enterotoxin, fragments and mutants or derivatives with adjuvant properties, oil-in-water and water-in-oil emulsions, toll-like receptor ligands such as muramyl dipeptide, *E. coli* LPS, oligonucleotides comprised of unmethylated DNA, poly I:C, lipoteichoic acid, peptidoglycan. Enterotoxins and their adjuvant active derivatives such as cholera toxin, heat-labile *E. coli* enterotoxin, pertussis toxin, shiga toxin and analogs. Other adjuvants can be used such as complete Freund's adjuvant, incomplete Freund's adjuvant, saponin, mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil or hydrocarbon emulsions, keyhole limpet hemocyanins, and potentially useful human adjuvants such as N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-nor-muramyl-L-alanyl-D-isoglutamine, N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-sn-glycero-3-hydroxyphosphoryloxy)-ethylamine, BCG (bacille Calmette-Guerin) and *Corynebacterium parvum*. An adjuvant can serve as a tissue depot that

slowly releases the antigen and also as a lymphoid system activator that non-specifically enhances the immune response (Hood et al., Immunology, Second Ed., 1984, Benjamin/Cummings: Menlo Park, Calif., p. 384). Where the vaccine is intended for use in human subjects, the adjuvant should be pharmaceutically acceptable.

Formulations

The compositions, vaccines and formulations of the present invention may comprise pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol); incorporation of the material into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hylauronic acid may also be used. See, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, Pa. 18042) pages 1435 1712 which are herein incorporated by reference.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants, preserving, wetting, emulsifying, and dispersing agents. The pharmaceutical compositions may be sterilized by, for example, filtration through a bacteria retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured using sterile water, or some other sterile injectable medium, immediately before use.

Administration and Dosage

The compositions (e.g., pharmaceutical or vaccine compositions) and formulations of the present invention can be administered topically, parenterally, orally, by inhalation, as a suppository, or by other methods known in the art. The term "parenteral" includes injection (for example, intravenous, intraperitoneal, epidural, intrathecal, intramuscular, intraluminal, intratracheal or subcutaneous). The preferred routes of administration are subcutaneous and intravenous.

The compositions and formulations of the present invention may be administered to an animal, preferably a mammal, and most preferably a human.

The dosage of the compositions or formulations of the present invention will vary widely, depending upon the nature of the disease, the patient's medical history, age, body weight, sex, sensitivity, the frequency of administration, the manner and route of administration, the clearance of the agent from the host, dosage period, drugs used in combination, and the like. The initial dose may be larger, followed by smaller maintenance doses.

For any composition or formulation used in the methods of the invention, the therapeutically effective dose can be estimated initially from animal models. Dose-response curves derived from animal systems are then used to determine testing doses for the initial clinical studies in humans. In safety determinations for each composition, the dose and frequency of administration should meet or exceed those anticipated for use in the clinical studies.

Toxicity and therapeutic efficacy of the compositions, vaccines, and formulations of the invention can be determined by standard pharmaceutical procedures in experimental animals, e.g., by determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index and it can be expressed as the ratio ED_{50}/LD_{50}. Compositions that exhibit large therapeutic indices are preferred.

The data obtained from the animal studies can be used in formulating a range of doses for use in humans. The therapeutically effective doses of in humans lay preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. Ideally, a single dose of each drug should be used daily.

The compositions of the invention will typically contain an effective amount of the compositions for achieving the desired effect. As used herein, an "effective amount of a glycopeptide" is an amount that elicits the desired response upon administration, e.g., an amount that elicits an immune response in a mammal.

Administration of the compositions or formulations of the invention may be once a day, twice a day, or more often, but frequency may be decreased during a maintenance phase of the disease or disorder, e.g., once every second or third day instead of every day or twice a day. The dose and the administration frequency will depend on the clinical signs, which confirm maintenance of the remission phase, with the reduction or absence of at least one or more preferably more than one clinical signs of the acute phase known to the person skilled in the art. More generally, dose and frequency will depend in part on recession of pathological signs and clinical and subclinical symptoms of a disease condition or disorder contemplated for treatment with the present compounds.

The appropriate dose and dosage times under certain conditions can be determined by the test based on the above-described indices but may be refined and ultimately decided according to the judgment of the practitioner and each patient's circumstances (age, general condition, severity of symptoms, sex, etc.) according to standard clinical techniques.

In certain embodiments of the invention, use of an appropriate vaccine design and immunization scheme will therefore elicit immunity to a glycopeptide epitope of the immunogen and efficiency of the immunization can be monitored by immunoassays, e.g., by detecting the presence of immunogen-specific antibodies in an antibody-containing sample from an immunized patient by ELISA or other assay suitable for detecting antigen-specific antibodies.

Keeping the above description in mind, typical dosages of the glycopeptide-containing compositions of the invention are 5-50 μg glycopeptides conjugated to e.g. KLH (keyhole-Limpet Hemocyanin) given subcutaneously 3-5 times with 2-3 weeks apart. Maintenance vaccine could be extended with monthly or bi-monthly dosing for extended periods.

Kits

In some embodiments, the invention relates to a kit comprising one or more glycopeptides identified by the present methods. In certain aspects the kit comprises a panel of two or more glycopeptides identified by the present methods. In other aspects, the kit further provides instructions for use. In a specific embodiment, the kit provides a diagnostic assay for diagnosing cancer, comprising a panel of cancer-associated glycopeptides, assay buffers, and instructions for use.

In accordance with the present invention, there may be employed conventional molecular biology, microbiology, recombinant DNA, immunology, cell biology and other

related techniques within the skill of the art. See, e.g., Sambrook et al., (2001) Molecular Cloning: A Laboratory Manual. 3rd ed. Cold Spring Harbor Laboratory Press: Cold Spring Harbor, N.Y.; Sambrook et al., (1989) Molecular Cloning: A Laboratory Manual. 2nd ed. Cold Spring Harbor Laboratory Press: Cold Spring Harbor, N.Y.; Ausubel et al., eds. (2005) Current Protocols in Molecular Biology. John Wiley and Sons, Inc.: Hoboken, N.J.; Bonifacino et al., eds. (2005) Current Protocols in Cell Biology. John Wiley and Sons, Inc.: Hoboken, N.J.; Coligan et al., eds. (2005) Current Protocols in Immunology, John Wiley and Sons, Inc.: Hoboken, N.J.; Coico et al., eds. (2005) Current Protocols in Microbiology, John Wiley and Sons, Inc.: Hoboken, N.J.; Coligan et al., eds. (2005) Current Protocols in Protein Science, John Wiley and Sons, Inc.: Hoboken, N.J.; Enna et al., eds. (2005) Current Protocols in Pharmacology John Wiley and Sons, Inc.: Hoboken, N.J.; Hames et al., eds. (1999) Protein Expression: A Practical Approach. Oxford University Press: Oxford; Freshney (2000) Culture of Animal Cells: A Manual of Basic Technique. 4th ed. Wiley-Liss; among others. The Current Protocols listed above are updated several times every year.

EXAMPLES

The present invention is described further below in working examples which are intended to further describe the invention without limiting the scope therein.

Example 1

Development of a Cancer-Associated O-Glycopeptide Library for Microarray Display

GalNAc-Ser/Thr-Fmoc amino acids were synthesized by Sussex Inc (Canada) and 20-mer peptides and corresponding glycopeptides with one GalNAc O-glycan synthesized and printed on epoxy activated glass slides by JPT Peptide Technologies (Berlin, Germany). A total of 48 paired peptides and 48 GalNAc-glycopeptides were synthesized and printed (Table II).

TABLE II

Synthetic 96 paired glycopeptide 20-mer library derived from confirmed O-glycoproteins*

SEQ ID NO:	Peptide No.	
4	1	TSAPDTRPAPGSTAPPAHGV
4	2	TSAPDTRPAPG**S**TAPPAHGV
5	3	SAPDTRPAPGSTAPPAHGVT
5	4	SAPDTRPAPGS**T**APPAHGVT
6	5	PGSTAPPAHGVTSAPDTRPA
6	6	PGSTAPPAHGV**T**SAPDTRPA
7	7	GSTAPPAHGVTSAPDTRPAP
7	8	GSTAPPAHGVT**S**APDTRPAP
8	9	PPAHGVTSAPDTRPAPGSTA
8	10	PPAHGVTSAPD**T**RPAPGSTA
9	11	FYLAMPFATPMEAELARRSL
10	12	KFSEFWDLDPEVRPTSAVAA
11	13	PLVEQGRVRAATVGSLAGQP
11	14	PLVEQGRVRAA**T**VGSLAGQP
12	15	LWSLCWSLAIATPLPPTSAH
12	16	LWSLCWSLAIA**T**PLPPTSAH
13	17	LEACVIQGVGVTETPLMKED
13	18	LEACVIQGVGV**T**ETPLMKED
14	19	KKWVQDSMKYLDQKSPTPKP
15	20	SHHSDESDELVTDFPTDLPA
15	21	SHHSDESDELV**T**DFPTDLPA
16	22	DESDELVTDFPTDLPATEVF
16	23	DESDELVTDFP**T**DLPATEVF
17	24	FPTDFPTDLPATEVFTPVVP
17	25	FPTDFPTDLPA**T**EVFTPVVP
18	26	FPTDLPATEVFTPVVPTVDT
18	27	FPTDLPATEVF**T**PVVPTVDT
19	28	PATEVFTPVVPTVDTYDGRG
19	29	PATEVFTPVVP**T**VDTYDGRG
20	30	PGAQGLPGVGLTPSAAQTAR
20	31	PGAQGLPGVGL**T**PSAAQTAR
21	32	RGETRCEQDRPSPTTAPPAP
21	33	RGETRCEQDRP**S**PTTAPPAP
22	34	ETRCEQDRPSPTTAPPAPPS
22	35	ETRCEQDRPSP**T**TAPPAPPS
23	36	TRCEQDRPSPTTAPPAPPSP
23	37	TRCEQDRPSPT**T**APPAPPSP
24	38	PSPTTAPPAPPSPSPSPVPK
24	39	PSPTTAPPAPP**S**PSPSPVPK
25	40	PTTAPPAPPSPSPSPVPKSP
25	41	PTTAPPAPPSP**S**PSPVPKSP
26	42	TAPPAPPSPSPSPVPKSPSV
26	43	TAPPAPPSPSP**S**PVPKSPSV
27	44	STNEFLCDKDKTSTVAPTIH
27	45	STNEFLCDKDK**T**STVAPTIH
28	46	NEFLCDKDKTSTVAPTIHTT
28	47	NEFLCDKDKTS**T**VAPTIHTT
29	48	CDKDKTSTVAPTIHTTVPSP
29	49	CDKDKTSTVAP**T**IHTTVPSP
30	50	DKTSTVAPTIHTTVPSPTTT
30	51	DKTSTVAPTIH**T**TVPSPTTT
31	52	KTSTVAPTIHTTVPSPTTTP
31	53	KTSTVAPTIHT**T**VPSPTTTP
32	54	TVAPTIHTTVPSPTTTPTPK
32	55	TVAPTIHTTVP**S**PTTTPTPK
33	56	APTIHTTVPSPTTTPTPKEK
33	57	APTIHTTVPSPT**T**TPTPKEK
34	58	PTIHTTVPSPTTTPTPKEKP
34	59	PTIHTTVPSPT**T**TPTPKEKP
35	60	TIHTTVPSPTTTPTPKEKPE
35	61	TIHTTVPSPTT**T**PTPKEKPE
36	62	TPTPKEKPEAGTYSVNNGND
36	63	TPTPKEKPEAG**T**YSVNNGND
37	64	ACLAVSAGPVPTPPDNIQVQ
37	65	ACLAVSAGPVP**T**PPDNIQVQ
38	66	RRAVLPQEEEGSGGGQLVTE
38	67	RRAVLPQEEEG**S**GGGQLVTE
39	68	LNAVNNSLTPQSTKVPSLFE
39	69	LNAVNNSLTPQ**S**TKVPSLFE
40	70	NAVNNSLTPQSTKVPSLFEF
40	71	NAVNNSLTPQS**T**KVPSLFEF
41	72	TFVLSALQPSPTHSSSNTQR
41	73	TFVLSALQPSP**T**HSSSNTQR
42	74	RQGWALRPVLPTQSAHDPPA
42	75	RQGWALRPVLP**T**QSAHDPPA
43	76	QKKAKNLDAITTPDPTTNAS
43	77	QKKAKNLDAIT**T**PDPTTNAS
44	78	FLSLSQGQESQTELPNPRIS
44	79	FLSLSQGQESQ**T**ELPNPRIS
45	80	LSLALVTNSAPTSSSTKKTQ
45	81	LSLALVTNSAP**T**SSSTKKTQ
46	82	LISPLAQAVRSSSRTPSDKP
46	83	LISPLAQAVRS**S**SRTPSDKP
47	84	DDENTAQFVHVSESFPHPGF
47	85	DDENTAQFVHV**S**ESFPHPGF
48	86	SESFPHPGFNMSLLENHTRQ
48	87	SESFPHPGFNM**S**LLENHTRQ
49	88	SGWGSIEPENFSFPDDLQCV
49	89	SGWGSIEPENF**S**FPDDLQCV
50	90	RIQRGPGRAFVTIGKIGNMR
50	91	RIQRGPGRAFV**T**IGKIGNMR
51	92	EMSRHSLEQKPTDAPPKVLT
51	93	EMSRHSLEQKP**T**DAPPKVLT
52	94	CSESLELEDPSSGLGVTKQD
52	95	CSESLELEDPS**S**GLGVTKQD
53	96	LLEFYLAMPFA**T**PMEAELAR

*Indicates attachment site of GalNAc residues to Ser/Thr (bold, underlined).

Glycopeptides were synthesized with and without N-terminal linker for printing on epoxy or NHS-activated glass slides, respectively. Peptides were designed based on known O-glycoproteins using the algorithm NetOGlyc for selection of O-glycosylation sites (Julenius et al. 2005), which in most cases coincides with experimentally determined O-glycosylation found on isolated proteins, as these glycoproteins have served as a training set for the algorithm. Glycopeptides were designed with a single GalNAc at position 12 to allow optimal exposure of peptide sequence flanking the O-glycan taking into consideration that the glycopeptides will be covalently linked primarily through the N-terminal amino acid. Glycopeptides were synthesized at 100 nmol scale using step-wise blocking by acetylation and printing directly with theoretical excess of 50 fold onto slides.

In one group, the paired peptide and single GalNAc glycopeptide library was further expanded by on-slide glycosylation with one or more recombinant glycosyltransferases to enhance the number of GalNAc O-glycosylation sites using one or more recombinant polypeptide GalNAc-transferases (e.g., GalNAc-T2, -T3 and -T4) (see, U.S. Pat. Nos. 5,876,716 and 6,465,220) (Bennett et al. 1998; Bennett et al. 1996; White et al. 1995)(see also, FIG. **1**). Further expansion was achieved by use of a recombinant sialyltransferase, ST6GalNAc-II, to produce STn glycoforms (structure no. 2, Table I) of the GalNAc glycopeptides. T glycoforms were produced by a recombinant *Drosophila* core1 β3galactosyltransferase, truncated core3 glycoforms (structure no. 6, Table I) were produced with a recombinant human β3GlcNAc-transferase (Iwai et al. 2002), and non-capped type1-core3 glycoforms (structure no. 9, Table I) were produced using β3Gal-T5 (see, U.S. Pat. No. 7,332,279).

Recombinant enzymes were expressed in insect cells using the baculo-virus system and used after semi-purification by Ni-chromatography (when HIS-tagged) or by ion exchange chromatographies. Glycosylation was monitored by staining of slides with lectins (HPA, VVA) (Sigma) and monoclonal antibodies to Tn (HBTn1, HBSTn1, HBT1) (Dako, Denmark). On-slide glycosylation was performed as follows: slides were quenched for 1 hr in 50 mM ethanolamine in 100 mM sodium borate pH 8, washed extensively in de-ionized water, and spun dry. Slides were blocked for 1 h with 1% BSA in PBS, pH 7.4, and in some cases with NP40 (1%) to reduce background. Slides were washed in PBS/0.05% Tween and enzyme reaction mixtures with BSA and detergent were applied and incubated 1-2 hrs at 37° C. Reaction mixtures for polypeptide GalNAc-transferases included MES buffer 125 mM, pH 7.4, 1% NP40, 1% BSA, 250 μM UDP-GalNAc, 2 mM $MnCl_2$ and 20 μg/mL enzyme. Reaction mixtures for galactosyltransferases included UDP-Gal, sialyltransferases CMP-NeuAc, GlcNAc-transferases UDP-GlcNAc. Following on-slide glycosylation slides were washed with PBS/Tween and processed with antibodies and lectins as described below.

It will be clear to one of ordinary skill in the art that on-slide glycosylation serves as a method to screen for additional glycoforms of peptides which may be recognized by autoantibodies present in patients. Once a particular glycoform of a given peptide is found to react with an autoantibody from a patient, the glycopeptide can be resynthesized in solution using the same enzymes used for on-slide glycosylation and the glycan structure and sites of attachment in the peptide confirmed by mass spectrometry (Tarp et al. 2007). The validated glycopeptide can then be incorporated into diagnostic panels as described throughout the specification and in Example 4.

FIG. **1** illustrates an example of on-slide glycosylation with the polypeptide GalNAc-transferase, GalNAc-T3, to glycosylate peptides and GalNAc glycopeptides having additional unsubstituted Ser/Thr residues to enhance the number of O-glycans. A library of 96 paired GalNAc-glycopeptides/peptides (20-mers with and without a single GalNAc residue at position 12), as designated in Table II, supra, were printed in triplicates (horizontal) on Scineon 16-well slides by JPT (Germany). In each pair in Table II, the glycopeptide of the pair contains a bold, underlined amino acid residue, indicating the site of attachment of GalNAc. Peptide pairs by peptide number are as follows: 1/2, 3/4, 5/6 . . . etc. The slide was reacted with the anti-Tn lectin HPA (1 μg/ml) without (FIG. **1**A) and with (FIG. **1**B) prior treatment with recombinant polypeptide GalNAc-T3 enzyme for on-slide GalNAc-glycosylation of available unglycosylated sites on peptides and glycopeptides.

The HPA lectin did not react with all GalNAc-glycopeptides (e.g., glycopeptide nos. 1-5 and 25-29), which is partly due to failure in synthesis and/or printing at these positions, as well as some restrictions of specificity of the GalNAc-binding lectin. The GalNAc-glycopeptides 1-5 did react with the HPA lectin in other experiments, and it was therefore concluded that there was a print failure. Conversion of peptides to GalNAc-glycopeptides by on-slide reaction with a polypeptide GalNAc-transferase is also expected to be dependent on the substrate specificity of the enzyme used, and, e.g., use of GalNAc-T2 rather than T3 may give a partly different labeling pattern.

Regardless, it is evident that most of the GalNAc-glycopeptides were labeled with HPA (FIG. **1**A) and that most of the corresponding paired peptides were labeled only after GalNAc-T3 on-slide glycosylation (FIG. **1**B). While HPA may not be expected to react with all GalNAc-glycopeptides, this lectin and other Tn reactive lectins such as HAA, VVA and DBA, as well as monoclonal anti-Tn antibodies (Dako) provide excellent controls for determining the quality of peptide synthesis and printing.

Example 2

High Through-Put Screening of Glycopeptide Microarrays with Human Serum for Identification of Glycopeptides Recognized by Cancer-Associated Auto-Antibodies

Sera Origin and Handling:

A panel of human sera was obtained from CHTN (Cooperative Human Tissue Network) and Asterand Inc., under the guidelines of approved agreements by the providers. Sera obtained were from control individuals ("normal") (n=31) and from newly diagnosed cancer patients (n=147) with pancreatic, breast, colon, lung, prostate or ovary primary cancers. Briefly, for cancer sera, all blood samples were obtained on or near date of diagnosis, and serum was processed immediately, flash frozen and stored at −70° C. until shipment. Serum samples received from the providers as frozen aliquots generally of 1-2 mL were brought to room temperature, vortexed and distributed into 20-100 μL aliquots in closeable Eppendorf tubes (vWR) (pre-labeled), and immediately frozen and stored at −70° C. until use.

Glycopeptide Microarray Method:

Glycopeptides (20-mers with and without a single GalNAc residue at position 12) and control structures (corresponding unglycosylated peptides) were printed on Corning (Corning, N.Y.), Scienion (Germany) or Schott Nexterion® Slide H or Schott Nexterion® Slide H MPX 16 (Schott AG, Mainz,

Germany) by JPT (Germany). Triplicates or quadruplicates of all compounds were printed at optimal concentrations (1-50 μM) or 50× excess relative to scale of synthesis for spot-synthesized glycopeptides printed without purification. After printing, slides were incubated for 1 hour (h) in a humidified hybridization chamber with 70-100% relative humidity and stored until use at 4° C. Unspotted slide areas were blocked for 1 h with 25 mM ethanolamine in 100 mM sodium borate pH 8.5. If an enzyme step was needed either to increase sites of GaLNac attachments in peptides or extend O-glycans to T, STn, core 3 or other structures, addition of the enzyme reaction mixture in 25-35 μL was made in appropriate wells and the slide incubated at 37° C. for 1 h, after which it was washed in PBS/0.05% Tween and then PBS, and then spun dry.

Human sera (usually diluted 1:25), monoclonal antibodies, lectins and the like were added in 25 μL and the slide left at room temperature for 2 h in a moist, humid chamber after which it was washed as above and spun dry (if no superstructure). Secondary antibodies were added at appropriate concentrations (for human sera, usually 1:1500 for anti-human IgG with a Cy3 chromophore). In some cases, for some controls, lectin-Cy3 was used directly as final step. The final step was washing as above, with a brief de-ionized water wash and the slide spun dry for scanning Analysis was made on a GenePix 4200AL Scanner at PMT 400 and power mode 10-50. Data were analyzed and plotted using Microsoft Excel.

Identification of Cancer-Associated Auto-Antibodies to GalNAc-Glycopeptide Epitopes:

Glycopeptides (20-mers with and without a single GalNAc residue at position 12) were printed in triplicates (horizontal) on Scineon 16-well slides by JPT (Germany) and bound human IgG antibodies detected by a labeled secondary anti-human IgG antibody. FIG. **2** illustrates examples of reactivities of serum (1:25 dilution) from a newly diagnosed prostate cancer patient (#762 in Panel A) and a normal control serum from a healthy individual (#174 in Panel B) on the library of 96 paired peptides/GalNAc-glycopeptides as designated in Table II. Candidate cancer-associated IgG antibodies identified in the cancer serum directed to GalNAc glycopeptide epitopes are indicated by open circles labeled 20/21, 62/63, and 86/87 for the paired peptide and GalNAc glycopeptides, respectively. The analysis demonstrates that serum of cancer patient contain IgG antibodies specifically reacting with epitopes found on GalNAc glycopeptides 21, 63, and 87, and since these antibodies do not react with the corresponding unglycosylated peptides 20, 62, and 86, it may be concluded that the epitopes are comprised of a GalNAc-peptide epitope including both the O-glycan part as well as part of the peptide sequence.

Human IgG antibodies from several cancers were shown to bind selectively to several GalNAc-glycopeptides and not the corresponding peptide, and such antibodies were not detected in healthy individuals. An example of this is shown in FIG. **2**, where a prostate cancer serum (prca#762) labels three GalNAc-glycopeptides (#21, 63, and 87), and not the corresponding peptide (#20, 62, and 86). These three candidates were also identified in other cancer sera but not in the controls as shown in FIGS. **3-5**, and described, infra.

FIG. **3** illustrates results of screening 147 cancer sera and 31 control sera (normal sera) on the glycopeptide pair #20/21. Sera obtained from newly diagnosed cancer patients with lung, colon, ovary, prostate, pancreas or breast tumors as well as controls (as indicated) were reacted with the 96-peptide array on Scineon 16-well slides (1:25 dilution) followed by cy3 labeled anti-human IgG (diluted to 1:1500). Arrays were analyzed on GenePix 4200 scanner at 400 pmt with 50 power and relative intensities graphed.

FIG. **4** illustrates results of screening 147 cancer sera and 31 normal sera on the glycopeptide pair #62/63. FIG. **5** illustrates results of screening 147 cancer sera and 31 normal sera on the glycopeptide pair #86/87.

Peptides 20/21, each having the sequence identified as SEQ ID NO: 15, are derived from SPP1 (Ensg00000118785) GenBank Accession No. NP_001035147 (SEQ ID NO: 61), peptides 62/63, each having the sequence identified as SEQ ID NO: 36 are derived from LAMP2 (Ensg00000005893) (ENST00000200639) protein (ENSP00000200639) GenBank Accession No. NP_002285 (SEQ ID NO: 64), and peptides 86/87, each having the sequence identified as SEQ ID NO: 49, are derived from KLK1 (gene: Ensg00000167748) (transcript: ENST00000301420) (protein: ENSP00000301420) (GenBank Accession No. NP_002248) (SEQ ID NO: 66). These proteins have broad expression patterns in tissues and hence may induce antibodies in many cancers.

The presented method using a limited glycopeptide library identified three candidate targets for human disease-associated auto-antibodies. These auto-antibody targets were defined by the discriminating factor that cancer-associated IgG antibodies reacted selectively with a glycopeptide and not the corresponding peptide or other glycopeptides with the same O-glycan or the O-glycan presented as a hapten on an artificial carrier.

Example 3

Generation of Antibodies to Identified Auto-Antibody Targets for Diagnostic Use

Monoclonal or polyclonal antibodies may be generated to the identified glycopeptide antigens by known methods (Takeuchi et al. 2002; Hanisch et al. 1995; Reis et al. 1998; Sorensen et al. 2006). Briefly, the following procedure serves as an example for generation of antibodies with the desired glycopeptides specificity but other procedures leading to the same result will be known to the skilled in the art.

Immunization Protocol:

Glycopeptides are coupled to keyhole limpet hemocyanin (KLH) (Pierce, Rockford, Ill.) using glutaraldehyde. Efficiency of conjugation is assessed by analyzing the reaction by size exclusion chromatography on a PD-10 column, where the conjugate/glycopeptides ratio can be determined by ELISA using appropriate reagents such as antibodies and lectins detecting the glycopeptides. Essentially all reactivity with a Tn reactive lectin (HPA) is found with the excluded fraction and insignificant reactivity in the included fractions expected to contain peptides. Titration analysis of the KLH conjugate with the corresponding glycopeptide in ELISA indicated conjugation ratio KLH to glycopeptide of approximately 1:200. Female Balb/c (Jackson Labs) wild type mice are injected subcutaneously with 10 or 15 μg of glycopeptide-KLH in a total volume of 200 μl (1:1 mix with Freunds adjuvant, Sigma). Mice received four immunizations 2-4 wks apart, and blood samples are obtained by tail or eye bleeding 1 wk following the third and fourth immunization.

Hybridoma Production:

Mouse hybridomas are produced by fusion of splenocytes to NS-1 followed by selection in HAT/HT (Hypoxanthine, Aminopterin, Thymidine). Hybridomas are selected by initial screening by ELISA with GalNAc-glycopeptides and corresponding peptides as well as irrelevant control compounds. Further characterization is done on glycopeptides microar-

rays as well as on a panel of human cancer cell lines expressing the corresponding aberrant glycoprotein.

Enzyme-linked immunosorbent assays (ELISA) are performed using 96-well MaxiSorp™ plates (Nunc). Plates are coated overnight at 4° C. with 1 μg/ml of glycopeptides in bicarbonate-carbonate buffer (pH 9.5), blocked with 5% BSA in PBS, followed by incubation with sera (diluted in PBS) or monoclonal antibodies for 2 hours (hrs) at room temperature. Bound antibodies are detected with peroxidase-conjugated rabbit anti-mouse immunoglobulins (Dako, Denmark) or isotype specific antibodies peroxidase-conjugated goat anti-mouse IgM, IgG1, IgG2a, IgG2b, or IgG3 (Southern Biotechnology Associates, USA). Plates are developed with o-phenylenediamine tablets (Dako, Denmark) and read at 492 nm. Control antibodies included anti-carbohydrate antibodies HBTn−1 (Tn) and HBSTn−1 (STn) (Dako) and lectins HPA, VVA and HAA (Sigma). Control sera included mice immunized with irrelevant peptides linked to KLH. Human cancer cell lines from different cancers are all obtained from ATCC and cultured as recommended by ATCC.

Immunocytochemical staining of cells are performed as follows: cells are harvested by trypsination, washed and plated onto multi-well glass slides and fixed for 10 minutes (min) in ice cold acetone or in methanol acetone. Fixed cells are incubated overnight at 4° C. with mouse sera (1:200/1:400/1:800) or hybridoma antibodies, followed by incubation for 45 min at room temperature with FITC-conjugated rabbit anti-mouse immunoglobulins (Dako, Denmark). Slides are mounted in glycerol containing p-phenylenediamine and examined in a fluorescence microscope.

For further determination of expression of glycopeptides epitope in human cancers immunohistochemistry of fixed and frozen tissue samples are performed. Frozen sections are fixed for 10 min in cold methanol/acetone (50:50). Formalin fixed, paraffin wax embedded tissues of different carcinoma and healthy tissues are obtained from Origine (US) and stained by immunofluorescence or peroxidase techniques. Paraffin sections are dewaxed, rehydrated, and treated with 0.5% H_2O_2 in methanol for 30 min. Section are rinsed in TBS and incubated for 20 min with rabbit nonimmune serum. Sections are rinsed and incubated overnight at 4° C. with primary antibody. Sections are rinsed and incubated with biotin-labeled rabbit anti-mouse serum (Dako, Denmark) diluted 1:200 in TBS for 30 min, rinsed with TBS, and incubated for 1 h with avidin-biotin-peroxidase complex (Dako, Denmark). Sections are rinsed with TBS and developed with 0.05% 3,3'-diaminobenzidine tetrahydrochloride freshly prepared in 0.05 M TBS containing 0.1% H_2O_2. Sections are stained with hematoxylin, dehydrated and mounted.

Example 4

Broad Discovery of O-Glycopeptide Epitopes

A larger library of GalNAc O-glycopeptides designed with GalNAc linked to serine or threonine at position 12 in 20-mer peptides was produced as described in Example 1. Peptides were selected among cell membrane and secreted human proteins that contain serine and threonine residues that are predicted to be O-glycosylated by the NetOGlyc algorithm (Julenius et al. 2005). A total of 960 GalNAc glycopeptides were synthesized at 0.5 mg scale (Sigma) and printed on microarray hydrogel slides (Schott Nexterion) as described in Example 1. Slides were reacted with human cancer sera (ovarian, breast, colon, lung, pancreas, prostate, 235 total sera) and control sera (145 healthy, 20 inflammatory, 20 benign tumor). Glycopeptides preferentially reactive with human IgG antibodies from cancer patients compared to controls were selected for resynthesis at 5 mg scale with amidated C-terminus (New England Peptide (Gardner, Mass.) (Table III). Resynthesized glycopeptides were reprinted on microarray slides at 50 μM and reacted with human cancer sera (Total 286 sera: 32 ovarian cancer (O), 38 breast cancer (B), 54 colon cancer (C), 17 lung cancer (L), and 145 age and sex matched control normal sera as described in Example 1. Table III lists glycopeptides exclusively or preferentially reactive with human IgG from cancer patients compared to controls and examples of reactivities are shown in FIG. **6**.

TABLE III

Glycopeptides reactive with IgG antibodies from human cancer sera

Peptide number	Sequence ID	Protein	Sequence
166	82	Oncostatin	H2N-TKAGRGASQPP**T**PTPASDAF-amide
113	83	gp95	H2N-EEEPEETAEDT**T**EDTEQDED-amide
218	84	MUC13	H2N-TASTTANTPFP**T**ATSPAPPI-amide
225	85	MUC13	H2N-PAPPIISTHSS**S**TIPTPAPP-amide
275a	86	Ceruplasm	H2N-LAKMYYSAVEP**T**KDIFTGLI-amide
284	87	CD46	H2N-PSSTKPPALSH**S**VSTSSTTK-amide
308	88	EBAG9	H2N-LEPDYFKDMTP**T**IRKTQKIV-amide
318a	89	MUC17	H2N-STMPVVSSEA**S**THSTTPVDT-amide
324	90	MUC17	H2N-STHSTTPVDTS**T**PVTTSTEA-amide
370	91	IL6-R	H2N-IPPEDTASTRS**S**FTVQDLKP-amide
382	92	R-PTP-alpha	H2N-EAKTSNPTSSL**T**SLSVAPTF-amide
389	93	R-PTP-alpha	H2N-ARTEPWEGNSS**T**AATTPETF-amide
443	94	ODAM	H2N-VDPLQLQTPPQ**T**QPGPSHVM-amide
450	95	ODAM	H2N-SPKPSTTNVFT**S**AVDQTITP-amide
456	96	IGFB-3	H2N-PAPPAPGNASE**S**EEDRSAGS-amide
458	97	IGFB-3	H2N-ASESEEDRSAG**S**VESPSVSS-amide
465	98	MUC15	H2N-ANLNSDKENIT**T**SNLKASHS-amide
484	99	MUC15	H2N-LTTNSDSFTGF**T**PYQEKTTL-amide
485	100	MUC15	H2N-SFTGFTPYQEK**T**TLQPTLKF-amide
485a	101	MUC15	H2N-SFTGFTPYQEKT**T**LQPTLKF-amide
505	102	TPBG Trophob	H2N-SPTSSASSFSS**S**APFLASAV-amide
522	103	IgAl hinge	H2N-TVPCPVPSTPPTP**S**PSTPPT-amide
524	104	IgAl hinge	H2N-VPSTPPTPSPS**T**PPTPSPSC-amide
544	105	R-PTP-N	H2N-SEPPKAARPPV**T**PVLLEKKS-amide
546	106	R-PTP-N	H2N-GQSQPTVAGQP**S**ARPAAEEY-amide

TABLE III-continued

Glycopeptides reactive with IgG antibodies from human cancer sera

Peptide number	Sequence ID	Protein	Sequence
558	107	CMRF35	H2N-TPASITAAKTS**T**ITTAFPPV-amide
569	108	TNF-RSF1B	H2N-GNASMDAVCTS**T**SPTRSMAP-amide
585	109	CGB2	H2N-TDCGGPKDHPL**T**CDDPRFQA-amide
587	110	CGB2	H2N-AQASSSSKAPPP**S**LPSPSRLP-amide
592	111	Acrosomal SP Cadherin 1	H2N-PLSELESGEQP**S**DEQPSGEH-amide
601	112	(CD)	H2N-PQRSSTAILQV**S**VTDTNDNH-amide
605	113	CD Ovomorolin	H2N-GALPGTSVMEV**T**ATDADDDV-amide
612	114	CD Mucin like	H2N-EQEPPSTDVPP**S**PEAGGTTG-amide
676	115	Inhibin alpha	H2N-RPEATPFLVAH**T**RTRPPSGG-amide
690	116	IGF-BP-6	H2N-PGTSTTPSQPN**S**AGVQDTEM-amide
739	117	LTBP1	H2N-EVAPEASTSSA**S**QVIAPTQV-amide
752	118	CD 248 Endosialin	H2N-QPPDFALAYRP**S**FPEDREPQ-amide
755	119	CD 248 Endosialin	H2N-LSVTRPVVVSA**T**HPTLPSAH-amide
757	120	CD 248 Endosialin	H2N-PSAHQPPVIPA**T**HPALSRDH-amide
765	121	CD 248 Endosialin	H2N-APDALVLRTQA**T**QLPIIPTA-amide
823	122	ICAM-1	H2N-GALFPGPGNAQ**T**SVSPSKVI-amide
827	123	ICAM-1	H2N-HLALGDQRLNP**T**VTYGNDSF-amide
827a	124	ICAM-1	H2N-HLALGDQRLNPTV**T**YGNDSF-amide
848	125	MUC1	H2N-PATEPASGSAA**T**WGQDVTSV-amide
852	126	MUC1	H2N-VPVTRPALGST**T**PPAHDVTS-amide
859	127	MUC1	H2N-NVTSASGSASG**S**ASTLVHNG-amide
859a	128	MUC1	H2N-NVTSASGSASGSA**S**TLVHNG-amide
863	129	MUC1	H2N-GTSARATTTPA**S**KSTPFSIP-amide
863a	130	MUC1	H2N-GTSARATTTPASK**S**TPFSIP-amide
870	131	MUC1	H2N-SDTPTTLASHS**T**KTDASSTH-amide
873	132	MUC1	H2N-TKTDASSTHHS**T**VPPLTSSN-amide
883	133	MUC1	H2N-TDYYQELQRDI**S**EMFLQIYK-amide
889	134	MUC1	H2N-HDVETQFNQYK**T**EAASRYNL-amide
893	135	MUC1	H2N-ASRYNLTISDV**S**VSDVPFPF-amide
894	136	MUC1	H2N-RYNLTISDVSV**S**DVPFPFSA-amide
895	137	MUC1	H2N-DVSVSDVPFPF**S**AQSGAGVP-amide
914	138	MUC4	H2N-TAGRPTGQSSP**T**SPSASPQE-amide
931	139	MUC4	H2N-SLASQATDIFS**T**VPPTPPSI-amide
934	140	MUC4	H2N-FSTVPPTPPSI**T**STGLTSPQ-amide
936	141	MUC4	H2N-PTPPSITSTGL**T**SPQTETHT-amide
941	142	MUC4	H2N-LTSPQTETHTL**S**PSGSGKTF-amide
977	143	MUC4	H2N-TDTSSASTGHA**T**PLPVTSLS-amide
983	144	MUC4	H2N-HATPLAVSSAT**S**ASTVSSDS-amide
852-C3	145	MUC1	H2N-VPVTRPALGST**T**[**GlcNAc**]PPAHDVTS-amide
931-C3	146	MUC4	H2N-SLASQATDIFS**T**[**GlcNAc**]**VPPT**PPSI-amide

*Bold S or T indicates attachment site of GalNAc residues to Ser/Thr; Bold [GlcNAc]indicates an addition of glucosamine attached to GalNAc (in bold). Bold, underlined name indicates peptide assayed in graphs in FIG. 6.

Since IgG antibodies reactive with glycopeptides epitopes recognize both the peptide sequence in close proximity to the O-glycan (i.e., one to five or even eighth residues N- and C-terminal of the O-glycan) as well as the O-glycan structure, it is clear that different glycoforms of one glycopeptide may be recognized by different IgG antibodies and these antibodies may be found in different cancer patients. In this Example, GalNAc-glycopeptides from MUC1 and MUC4 were also produced as the core 3 GlcNAcβ1-3GalNAcα1-O-Ser/Thr glycoform with a recombinant core 3 synthase as described in Example 1. Two core 3 glycopeptides (#852-C3 and #931-C3) were identified as exclusively recognized by IgG antibodies in sera from cancer patients.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

It is further to be understood that all values are approximate, and are provided for description.

Patents, patent applications, publications, product descriptions, and protocols are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties for all purposes.

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Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
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Thr Glu Lys Asn Ala Leu Ser Thr Gly Val Ser Phe Phe Phe Leu Ser
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Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp Pro Ser
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Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu
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Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe
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Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser
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Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly
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Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu Ala
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Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn
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Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met
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Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala
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Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Phe Asn
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Ser Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg
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Asp Ile Ser Glu Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu
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Gly Leu Ser Asn Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu
            100                 105                 110

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Gln Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr
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Ile Ser Asp Val Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln
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Ser Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val
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Cys Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val
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Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala
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Thr Glu Lys Asn Ala Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp
50 55 60

Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu Gln Ile
65 70 75 80

Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe Arg Pro
85 90 95

Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly Thr Ile
100 105 110

Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala
115 120 125

Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val
130 135 140

Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly Trp Gly
145 150 155 160

Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu Ala Ile Val
165 170 175

Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly
180 185 190

Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu
195 200 205

Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr
210 215 220

Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser
225 230 235 240

Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu
245 250 255

<210> SEQ ID NO 4
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 4

Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro
1 5 10 15

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Ala His Gly Val
20

<210> SEQ ID NO 5
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 5

Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala
1 5 10 15

His Gly Val Thr
20

<210> SEQ ID NO 6
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 6

Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp
1 5 10 15

Thr Arg Pro Ala
20

<210> SEQ ID NO 7
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 7

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
1 5 10 15

Arg Pro Ala Pro
20

<210> SEQ ID NO 8
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 8

Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
1 5 10 15

Gly Ser Thr Ala
20

<210> SEQ ID NO 9
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 9

Phe Tyr Leu Ala Met Pro Phe Ala Thr Pro Met Glu Ala Glu Leu Ala

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1 5 10 15

Arg Arg Ser Leu
20

<210> SEQ ID NO 10
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 10

Lys Phe Ser Glu Phe Trp Asp Leu Asp Pro Glu Val Arg Pro Thr Ser
1 5 10 15

Ala Val Ala Ala
20

<210> SEQ ID NO 11
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 11

Pro Leu Val Glu Gln Gly Arg Val Arg Ala Ala Thr Val Gly Ser Leu
1 5 10 15

Ala Gly Gln Pro
20

<210> SEQ ID NO 12
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 12

Leu Trp Ser Leu Cys Trp Ser Leu Ala Ile Ala Thr Pro Leu Pro Pro
1 5 10 15

Thr Ser Ala His
20

<210> SEQ ID NO 13
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 13

Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu
1 5 10 15

Met Lys Glu Asp
20

<210> SEQ ID NO 14
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 14

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Lys Lys Trp Val Gln Asp Ser Met Lys Tyr Leu Asp Gln Lys Ser Pro
1 5 10 15

Thr Pro Lys Pro
20

<210> SEQ ID NO 15
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 15

Ser His His Ser Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr
1 5 10 15

Asp Leu Pro Ala
20

<210> SEQ ID NO 16
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 16

Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala
1 5 10 15

Thr Glu Val Phe
20

<210> SEQ ID NO 17
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 17

Phe Pro Thr Asp Phe Pro Thr Asp Leu Pro Ala Thr Glu Val Phe Thr
1 5 10 15

Pro Val Val Pro
20

<210> SEQ ID NO 18
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 18

Phe Pro Thr Asp Leu Pro Ala Thr Glu Val Phe Thr Pro Val Val Pro
1 5 10 15

Thr Val Asp Thr
20

<210> SEQ ID NO 19
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 19

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Pro Ala Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr
1 5 10 15

Asp Gly Arg Gly
20

<210> SEQ ID NO 20
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 20

Pro Gly Ala Gln Gly Leu Pro Gly Val Gly Leu Thr Pro Ser Ala Ala
1 5 10 15

Gln Thr Ala Arg
20

<210> SEQ ID NO 21
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 21

Arg Gly Glu Thr Arg Cys Glu Gln Asp Arg Pro Ser Pro Thr Thr Ala
1 5 10 15

Pro Pro Ala Pro
20

<210> SEQ ID NO 22
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 22

Glu Thr Arg Cys Glu Gln Asp Arg Pro Ser Pro Thr Thr Ala Pro Pro
1 5 10 15

Ala Pro Pro Ser
20

<210> SEQ ID NO 23
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 23

Thr Arg Cys Glu Gln Asp Arg Pro Ser Pro Thr Thr Ala Pro Pro Ala
1 5 10 15

Pro Pro Ser Pro
20

<210> SEQ ID NO 24
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

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<400> SEQUENCE: 24

Pro Ser Pro Thr Thr Ala Pro Pro Ala Pro Pro Ser Pro Ser Pro Ser
1 5 10 15

Pro Val Pro Lys
20

<210> SEQ ID NO 25
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 25

Pro Thr Thr Ala Pro Pro Ala Pro Pro Ser Pro Ser Pro Ser Pro Val
1 5 10 15

Pro Lys Ser Pro
20

<210> SEQ ID NO 26
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 26

Thr Ala Pro Pro Ala Pro Pro Ser Pro Ser Pro Ser Pro Val Pro Lys
1 5 10 15

Ser Pro Ser Val
20

<210> SEQ ID NO 27
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 27

Ser Thr Asn Glu Phe Leu Cys Asp Lys Asp Lys Thr Ser Thr Val Ala
1 5 10 15

Pro Thr Ile His
20

<210> SEQ ID NO 28
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 28

Asn Glu Phe Leu Cys Asp Lys Asp Lys Thr Ser Thr Val Ala Pro Thr
1 5 10 15

Ile His Thr Thr
20

<210> SEQ ID NO 29
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

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<400> SEQUENCE: 29

Cys Asp Lys Asp Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr
1 5 10 15

Val Pro Ser Pro
20

<210> SEQ ID NO 30
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 30

Asp Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser
1 5 10 15

Pro Thr Thr Thr
20

<210> SEQ ID NO 31
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 31

Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro
1 5 10 15

Thr Thr Thr Pro
20

<210> SEQ ID NO 32
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 32

Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro Thr Thr Thr
1 5 10 15

Pro Thr Pro Lys
20

<210> SEQ ID NO 33
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 33

Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro Thr Thr Thr Pro Thr
1 5 10 15

Pro Lys Glu Lys
20

<210> SEQ ID NO 34
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 34

Pro Thr Ile His Thr Thr Val Pro Ser Pro Thr Thr Thr Pro Thr Pro
1 5 10 15

Lys Glu Lys Pro
20

<210> SEQ ID NO 35
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 35

Thr Ile His Thr Thr Val Pro Ser Pro Thr Thr Thr Pro Thr Pro Lys
1 5 10 15

Glu Lys Pro Glu
20

<210> SEQ ID NO 36
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 36

Thr Pro Thr Pro Lys Glu Lys Pro Glu Ala Gly Thr Tyr Ser Val Asn
1 5 10 15

Asn Gly Asn Asp
20

<210> SEQ ID NO 37
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 37

Ala Cys Leu Ala Val Ser Ala Gly Pro Val Pro Thr Pro Pro Asp Asn
1 5 10 15

Ile Gln Val Gln
20

<210> SEQ ID NO 38
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 38

Arg Arg Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly Gly Gly Gln
1 5 10 15

Leu Val Thr Glu
20

<210> SEQ ID NO 39
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 39

Leu Asn Ala Val Asn Asn Ser Leu Thr Pro Gln Ser Thr Lys Val Pro
1 5 10 15

Ser Leu Phe Glu
20

<210> SEQ ID NO 40
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 40

Asn Ala Val Asn Asn Ser Leu Thr Pro Gln Ser Thr Lys Val Pro Ser
1 5 10 15

Leu Phe Glu Phe
20

<210> SEQ ID NO 41
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 41

Thr Phe Val Leu Ser Ala Leu Gln Pro Ser Pro Thr His Ser Ser Ser
1 5 10 15

Asn Thr Gln Arg
20

<210> SEQ ID NO 42
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 42

Arg Gln Gly Trp Ala Leu Arg Pro Val Leu Pro Thr Gln Ser Ala His
1 5 10 15

Asp Pro Pro Ala
20

<210> SEQ ID NO 43
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 43

Gln Lys Lys Ala Lys Asn Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr
1 5 10 15

Thr Asn Ala Ser
20

<210> SEQ ID NO 44
<211> LENGTH: 20
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 44

Phe Leu Ser Leu Ser Gln Gly Gln Glu Ser Gln Thr Glu Leu Pro Asn
1 5 10 15

Pro Arg Ile Ser
20

<210> SEQ ID NO 45
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 45

Leu Ser Leu Ala Leu Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr
1 5 10 15

Lys Lys Thr Gln
20

<210> SEQ ID NO 46
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 46

Leu Ile Ser Pro Leu Ala Gln Ala Val Arg Ser Ser Ser Arg Thr Pro
1 5 10 15

Ser Asp Lys Pro
20

<210> SEQ ID NO 47
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 47

Asp Asp Glu Asn Thr Ala Gln Phe Val His Val Ser Glu Ser Phe Pro
1 5 10 15

His Pro Gly Phe
20

<210> SEQ ID NO 48
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 48

Ser Glu Ser Phe Pro His Pro Gly Phe Asn Met Ser Leu Leu Glu Asn
1 5 10 15

His Thr Arg Gln
20

<210> SEQ ID NO 49
<211> LENGTH: 20

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 49

Ser Gly Trp Gly Ser Ile Glu Pro Glu Asn Phe Ser Phe Pro Asp Asp
1 5 10 15

Leu Gln Cys Val
20

<210> SEQ ID NO 50
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 50

Arg Ile Gln Arg Gly Pro Gly Arg Ala Phe Val Thr Ile Gly Lys Ile
1 5 10 15

Gly Asn Met Arg
20

<210> SEQ ID NO 51
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 51

Glu Met Ser Arg His Ser Leu Glu Gln Lys Pro Thr Asp Ala Pro Pro
1 5 10 15

Lys Val Leu Thr
20

<210> SEQ ID NO 52
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 52

Cys Ser Glu Ser Leu Glu Leu Glu Asp Pro Ser Ser Gly Leu Gly Val
1 5 10 15

Thr Lys Gln Asp
20

<210> SEQ ID NO 53
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 53

Leu Leu Glu Phe Tyr Leu Ala Met Pro Phe Ala Thr Pro Met Glu Ala
1 5 10 15

Glu Leu Ala Arg
20

<210> SEQ ID NO 54

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<211> LENGTH: 203
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
35 40 45

Thr Glu Lys Asn Ala Ile Pro Ala Pro Thr Thr Thr Lys Ser Cys Arg
50 55 60

Glu Thr Phe Leu Lys Cys Phe Cys Arg Phe Ile Asn Lys Gly Val Phe
65 70 75 80

Trp Ala Ser Pro Ile Leu Ser Ser Val Ser Asp Val Pro Phe Pro Phe
85 90 95

Ser Ala Gln Ser Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu
100 105 110

Val Leu Val Cys Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala
115 120 125

Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile
130 135 140

Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr
145 150 155 160

His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro
165 170 175

Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr
180 185 190

Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu
195 200

<210> SEQ ID NO 55
<211> LENGTH: 150
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
35 40 45

Thr Glu Lys Asn Ala Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp
50 55 60

Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Ala Val Cys Gln
65 70 75 80

Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp
85 90 95

Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg
100 105 110

Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser
115 120 125

Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala
130 135 140

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Ala Thr Ser Ala Asn Leu
145 150

<210> SEQ ID NO 56
<211> LENGTH: 159
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr
1 5 10 15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly
20 25 30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala
35 40 45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Phe Asn
50 55 60

Ser Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg
65 70 75 80

Asp Ile Ser Glu Met Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly
85 90 95

Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu
100 105 110

Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr
115 120 125

Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser
130 135 140

Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu
145 150 155

<210> SEQ ID NO 57
<211> LENGTH: 14507
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

Met Leu Lys Pro Ser Gly Leu Pro Gly Ser Ser Ser Pro Thr Arg Ser
1 5 10 15

Leu Met Thr Gly Ser Arg Ser Thr Lys Ala Thr Pro Glu Met Asp Ser
20 25 30

Gly Leu Thr Gly Ala Thr Leu Ser Pro Lys Thr Ser Thr Gly Ala Ile
35 40 45

Val Val Thr Glu His Thr Leu Pro Phe Thr Ser Pro Asp Lys Thr Leu
50 55 60

Ala Ser Pro Thr Ser Ser Val Val Gly Arg Thr Thr Gln Ser Leu Gly
65 70 75 80

Val Met Ser Ser Ala Leu Pro Glu Ser Thr Ser Arg Gly Met Thr His
85 90 95

Ser Glu Gln Arg Thr Ser Pro Ser Leu Ser Pro Gln Val Asn Gly Thr
100 105 110

Pro Ser Arg Asn Tyr Pro Ala Thr Ser Met Val Ser Gly Leu Ser Ser
115 120 125

Pro Arg Thr Arg Thr Ser Ser Thr Glu Gly Asn Phe Thr Lys Glu Ala
130 135 140

Ser Thr Tyr Thr Leu Thr Val Glu Thr Thr Ser Gly Pro Val Thr Glu
145 150 155 160

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Lys Tyr Thr Val Pro Thr Glu Thr Ser Thr Thr Glu Gly Asp Ser Thr
                165                 170                 175

Glu Thr Pro Trp Asp Thr Arg Tyr Ile Pro Val Lys Ile Thr Ser Pro
            180                 185                 190

Met Lys Thr Phe Ala Asp Ser Thr Ala Ser Lys Glu Asn Ala Pro Val
        195                 200                 205

Ser Met Thr Pro Ala Glu Thr Thr Val Thr Asp Ser His Thr Pro Gly
    210                 215                 220

Arg Thr Asn Pro Ser Phe Gly Thr Leu Tyr Ser Ser Phe Leu Asp Leu
225                 230                 235                 240

Ser Pro Lys Gly Thr Pro Asn Ser Arg Gly Glu Thr Ser Leu Glu Leu
                245                 250                 255

Ile Leu Ser Thr Thr Gly Tyr Pro Phe Ser Ser Pro Glu Pro Gly Ser
            260                 265                 270

Ala Gly His Ser Arg Ile Ser Thr Ser Ala Pro Leu Ser Ser Ser Ala
        275                 280                 285

Ser Val Leu Asp Asn Lys Ile Ser Glu Thr Ser Ile Phe Ser Gly Gln
    290                 295                 300

Ser Leu Thr Ser Pro Leu Ser Pro Gly Val Pro Glu Ala Arg Ala Ser
305                 310                 315                 320

Thr Met Pro Asn Ser Ala Ile Pro Phe Ser Met Thr Leu Ser Asn Ala
                325                 330                 335

Glu Thr Ser Ala Glu Arg Val Arg Ser Thr Ile Ser Ser Leu Gly Thr
            340                 345                 350

Pro Ser Ile Ser Thr Lys Gln Thr Ala Glu Thr Ile Leu Thr Phe His
        355                 360                 365

Ala Phe Ala Glu Thr Met Asp Ile Pro Ser Thr His Ile Ala Lys Thr
    370                 375                 380

Leu Ala Ser Glu Trp Leu Gly Ser Pro Gly Thr Leu Gly Gly Thr Ser
385                 390                 395                 400

Thr Ser Ala Leu Thr Thr Thr Ser Pro Ser Thr Thr Leu Val Ser Glu
                405                 410                 415

Glu Thr Asn Thr His His Ser Thr Ser Gly Lys Glu Thr Glu Gly Thr
            420                 425                 430

Leu Asn Thr Ser Met Thr Pro Leu Glu Thr Ser Ala Pro Gly Glu Glu
        435                 440                 445

Ser Glu Met Thr Ala Thr Leu Val Pro Thr Leu Gly Phe Thr Thr Leu
    450                 455                 460

Asp Ser Lys Ile Arg Ser Pro Ser Gln Val Ser Ser Ser His Pro Thr
465                 470                 475                 480

Arg Glu Leu Arg Thr Thr Gly Ser Thr Ser Gly Arg Gln Ser Ser Ser
                485                 490                 495

Thr Ala Ala His Gly Ser Ser Asp Ile Leu Arg Ala Thr Thr Ser Ser
            500                 505                 510

Thr Ser Lys Ala Ser Ser Trp Thr Ser Glu Ser Thr Ala Gln Gln Phe
        515                 520                 525

Ser Glu Pro Gln His Thr Gln Trp Val Glu Thr Ser Pro Ser Met Lys
    530                 535                 540

Thr Glu Arg Pro Pro Ala Ser Thr Ser Val Ala Ala Pro Ile Thr Thr
545                 550                 555                 560

Ser Val Pro Ser Val Val Ser Gly Phe Thr Thr Leu Lys Thr Ser Ser
                565                 570                 575
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Thr Lys Gly Ile Trp Leu Glu Glu Thr Ser Ala Asp Thr Leu Ile Gly
            580                 585                 590

Glu Ser Thr Ala Gly Pro Thr Thr His Gln Phe Ala Val Pro Thr Gly
        595                 600                 605

Ile Ser Met Thr Gly Gly Ser Ser Thr Arg Gly Ser Gln Gly Thr Thr
    610                 615                 620

His Leu Leu Thr Arg Ala Thr Ala Ser Ser Glu Thr Ser Ala Asp Leu
625                 630                 635                 640

Thr Leu Ala Thr Asn Gly Val Pro Val Ser Val Ser Pro Ala Val Ser
                645                 650                 655

Lys Thr Ala Ala Gly Ser Ser Pro Pro Gly Gly Thr Lys Pro Ser Tyr
            660                 665                 670

Thr Met Val Ser Ser Val Ile Pro Glu Thr Ser Ser Leu Gln Ser Ser
        675                 680                 685

Ala Phe Arg Glu Gly Thr Ser Leu Gly Leu Thr Pro Leu Asn Thr Arg
    690                 695                 700

His Pro Phe Ser Ser Pro Glu Pro Asp Ser Ala Gly His Thr Lys Ile
705                 710                 715                 720

Ser Thr Ser Ile Pro Leu Leu Ser Ser Ala Ser Val Leu Glu Asp Lys
                725                 730                 735

Val Ser Ala Thr Ser Thr Phe Ser His His Lys Ala Thr Ser Ser Ile
            740                 745                 750

Thr Thr Gly Thr Pro Glu Ile Ser Thr Lys Thr Lys Pro Ser Ser Ala
        755                 760                 765

Val Leu Ser Ser Met Thr Leu Ser Asn Ala Ala Thr Ser Pro Glu Arg
    770                 775                 780

Val Arg Asn Ala Thr Ser Pro Leu Thr His Pro Ser Pro Ser Gly Glu
785                 790                 795                 800

Glu Thr Ala Gly Ser Val Leu Thr Leu Ser Thr Ser Ala Glu Thr Thr
                805                 810                 815

Asp Ser Pro Asn Ile His Pro Thr Gly Thr Leu Thr Ser Glu Ser Ser
            820                 825                 830

Glu Ser Pro Ser Thr Leu Ser Leu Pro Ser Val Ser Gly Val Lys Thr
        835                 840                 845

Thr Phe Ser Ser Ser Thr Pro Ser Thr His Leu Phe Thr Ser Gly Glu
    850                 855                 860

Glu Thr Glu Glu Thr Ser Asn Pro Ser Val Ser Gln Pro Glu Thr Ser
865                 870                 875                 880

Val Ser Arg Val Arg Thr Thr Leu Ala Ser Thr Ser Val Pro Thr Pro
                885                 890                 895

Val Phe Pro Thr Met Asp Thr Trp Pro Thr Arg Ser Ala Gln Phe Ser
            900                 905                 910

Ser Ser His Leu Val Ser Glu Leu Arg Ala Thr Ser Ser Thr Ser Val
        915                 920                 925

Thr Asn Ser Thr Gly Ser Ala Leu Pro Lys Ile Ser His Leu Thr Gly
    930                 935                 940

Thr Ala Thr Met Ser Gln Thr Asn Arg Asp Thr Phe Asn Asp Ser Ala
945                 950                 955                 960

Ala Pro Gln Ser Thr Thr Trp Pro Glu Thr Ser Pro Arg Phe Lys Thr
                965                 970                 975

Gly Leu Pro Ser Ala Thr Thr Thr Val Ser Thr Ser Ala Thr Ser Leu
            980                 985                 990

Ser Ala Thr Val Met Val Ser Lys  Phe Thr Ser Pro Ala  Thr Ser Ser
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        995                 1000                1005

Met Glu  Ala Thr Ser Ile Arg  Glu Pro Ser Thr Thr  Ile Leu Thr
    1010                1015                1020

Thr Glu  Thr Thr Asn Gly Pro  Gly Ser Met Ala Val  Ala Ser Thr
    1025                1030                1035

Asn Ile  Pro Ile Gly Lys Gly  Tyr Ile Thr Glu Gly  Arg Leu Asp
    1040                1045                1050

Thr Ser  His Leu Pro Ile Gly  Thr Thr Ala Ser Ser  Glu Thr Ser
    1055                1060                1065

Met Asp  Phe Thr Met Ala Lys  Glu Ser Val Ser Met  Ser Val Ser
    1070                1075                1080

Pro Ser  Gln Ser Met Asp Ala  Ala Gly Ser Ser Thr  Pro Gly Arg
    1085                1090                1095

Thr Ser  Gln Phe Val Asp Thr  Phe Ser Asp Asp Val  Tyr His Leu
    1100                1105                1110

Thr Ser  Arg Glu Ile Thr Ile  Pro Arg Asp Gly Thr  Ser Ser Ala
    1115                1120                1125

Leu Thr  Pro Gln Met Thr Ala  Thr His Pro Pro Ser  Pro Asp Pro
    1130                1135                1140

Gly Ser  Ala Arg Ser Thr Trp  Leu Gly Ile Leu Ser  Ser Ser Pro
    1145                1150                1155

Ser Ser  Pro Thr Pro Lys Val  Thr Met Ser Ser Thr  Phe Ser Thr
    1160                1165                1170

Gln Arg  Val Thr Thr Ser Met  Ile Met Asp Thr Val  Glu Thr Ser
    1175                1180                1185

Arg Trp  Asn Met Pro Asn Leu  Pro Ser Thr Thr Ser  Leu Thr Pro
    1190                1195                1200

Ser Asn  Ile Pro Thr Ser Gly  Ala Ile Gly Lys Ser  Thr Leu Val
    1205                1210                1215

Pro Leu  Asp Thr Pro Ser Pro  Ala Thr Ser Leu Glu  Ala Ser Glu
    1220                1225                1230

Gly Gly  Leu Pro Thr Leu Ser  Thr Tyr Pro Glu Ser  Thr Asn Thr
    1235                1240                1245

Pro Ser  Ile His Leu Gly Ala  His Ala Ser Ser Glu  Ser Pro Ser
    1250                1255                1260

Thr Ile  Lys Leu Thr Met Ala  Ser Val Val Lys Pro  Gly Ser Tyr
    1265                1270                1275

Thr Pro  Leu Thr Phe Pro Ser  Ile Glu Thr His Ile  His Val Ser
    1280                1285                1290

Thr Ala  Arg Met Ala Tyr Ser  Ser Gly Ser Ser Pro  Glu Met Thr
    1295                1300                1305

Ala Pro  Gly Glu Thr Asn Thr  Gly Ser Thr Trp Asp  Pro Thr Thr
    1310                1315                1320

Tyr Ile  Thr Thr Thr Asp Pro  Lys Asp Thr Ser Ser  Ala Gln Val
    1325                1330                1335

Ser Thr  Pro His Ser Val Arg  Thr Leu Arg Thr Thr  Glu Asn His
    1340                1345                1350

Pro Lys  Thr Glu Ser Ala Thr  Pro Ala Ala Tyr Ser  Gly Ser Pro
    1355                1360                1365

Lys Ile  Ser Ser Ser Pro Asn  Leu Thr Ser Pro Ala  Thr Lys Ala
    1370                1375                1380

Trp Thr  Ile Thr Asp Thr Thr  Glu His Ser Thr Gln  Leu His Tyr
    1385                1390                1395
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Thr Lys  Leu Ala Glu Lys Ser  Ser Gly Phe Glu Thr  Gln Ser Ala
    1400                 1405                 1410

Pro Gly  Pro Val Ser Val Val  Ile Pro Thr Ser Pro  Thr Ile Gly
    1415                 1420                 1425

Ser Ser  Thr Leu Glu Leu Thr  Ser Asp Val Pro Gly  Glu Pro Leu
    1430                 1435                 1440

Val Leu  Ala Pro Ser Glu Gln  Thr Thr Ile Thr Leu  Pro Met Ala
    1445                 1450                 1455

Thr Trp  Leu Ser Thr Ser Leu  Thr Glu Glu Met Ala  Ser Thr Asp
    1460                 1465                 1470

Leu Asp  Ile Ser Ser Pro Ser  Ser Pro Met Ser Thr  Phe Ala Ile
    1475                 1480                 1485

Phe Pro  Pro Met Ser Thr Pro  Ser His Glu Leu Ser  Lys Ser Glu
    1490                 1495                 1500

Ala Asp  Thr Ser Ala Ile Arg  Asn Thr Asp Ser Thr  Thr Leu Asp
    1505                 1510                 1515

Gln His  Leu Gly Ile Arg Ser  Leu Gly Arg Thr Gly  Asp Leu Thr
    1520                 1525                 1530

Thr Val  Pro Ile Thr Pro Leu  Thr Thr Thr Trp Thr  Ser Val Ile
    1535                 1540                 1545

Glu His  Ser Thr Gln Ala Gln  Asp Thr Leu Ser Ala  Thr Met Ser
    1550                 1555                 1560

Pro Thr  His Val Thr Gln Ser  Leu Lys Asp Gln Thr  Ser Ile Pro
    1565                 1570                 1575

Ala Ser  Ala Ser Pro Ser His  Leu Thr Glu Val Tyr  Pro Glu Leu
    1580                 1585                 1590

Gly Thr  Gln Gly Arg Ser Ser  Ser Glu Ala Thr Thr  Phe Trp Lys
    1595                 1600                 1605

Pro Ser  Thr Asp Thr Leu Ser  Arg Glu Ile Glu Thr  Gly Pro Thr
    1610                 1615                 1620

Asn Ile  Gln Ser Thr Pro Pro  Met Asp Asn Thr Thr  Thr Gly Ser
    1625                 1630                 1635

Ser Ser  Ser Gly Val Thr Leu  Gly Ile Ala His Leu  Pro Ile Gly
    1640                 1645                 1650

Thr Ser  Ser Pro Ala Glu Thr  Ser Thr Asn Met Ala  Leu Glu Arg
    1655                 1660                 1665

Arg Ser  Ser Thr Ala Thr Val  Ser Met Ala Gly Thr  Met Gly Leu
    1670                 1675                 1680

Leu Val  Thr Ser Ala Pro Gly  Arg Ser Ile Ser Gln  Ser Leu Gly
    1685                 1690                 1695

Arg Val  Ser Ser Val Leu Ser  Glu Ser Thr Thr Glu  Gly Val Thr
    1700                 1705                 1710

Asp Ser  Ser Lys Gly Ser Ser  Pro Arg Leu Asn Thr  Gln Gly Asn
    1715                 1720                 1725

Thr Ala  Leu Ser Ser Ser Leu  Glu Pro Ser Tyr Ala  Glu Gly Ser
    1730                 1735                 1740

Gln Met  Ser Thr Ser Ile Pro  Leu Thr Ser Ser Pro  Thr Thr Pro
    1745                 1750                 1755

Asp Val  Glu Phe Ile Gly Gly  Ser Thr Phe Trp Thr  Lys Glu Val
    1760                 1765                 1770

Thr Thr  Val Met Thr Ser Asp  Ile Ser Lys Ser Ser  Ala Arg Thr
    1775                 1780                 1785
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Glu Ser  Ser Ser Ala Thr Leu  Met Ser Thr Ala Leu  Gly Ser Thr
    1790                 1795                 1800

Glu Asn  Thr Gly Lys Glu Lys  Leu Arg Thr Ala Ser  Met Asp Leu
    1805                 1810                 1815

Pro Ser  Pro Thr Pro Ser Met  Glu Val Thr Pro Trp  Ile Ser Leu
    1820                 1825                 1830

Thr Leu  Ser Asn Ala Pro Asn  Thr Thr Asp Ser Leu  Asp Leu Ser
    1835                 1840                 1845

His Gly  Val His Thr Ser Ser  Ala Gly Thr Leu Ala  Thr Asp Arg
    1850                 1855                 1860

Ser Leu  Asn Thr Gly Val Thr  Arg Ala Ser Arg Leu  Glu Asn Gly
    1865                 1870                 1875

Ser Asp  Thr Ser Ser Lys Ser  Leu Ser Met Gly Asn  Ser Thr His
    1880                 1885                 1890

Thr Ser  Met Thr Tyr Thr Glu  Lys Ser Glu Val Ser  Ser Ser Ile
    1895                 1900                 1905

His Pro  Arg Pro Glu Thr Ser  Ala Pro Gly Ala Glu  Thr Thr Leu
    1910                 1915                 1920

Thr Ser  Thr Pro Gly Asn Arg  Ala Ile Ser Leu Thr  Leu Pro Phe
    1925                 1930                 1935

Ser Ser  Ile Pro Val Glu Glu  Val Ile Ser Thr Gly  Ile Thr Ser
    1940                 1945                 1950

Gly Pro  Asp Ile Asn Ser Ala  Pro Met Thr His Ser  Pro Ile Thr
    1955                 1960                 1965

Pro Pro  Thr Ile Val Trp Thr  Ser Thr Gly Thr Ile  Glu Gln Ser
    1970                 1975                 1980

Thr Gln  Pro Leu His Ala Val  Ser Ser Glu Lys Val  Ser Val Gln
    1985                 1990                 1995

Thr Gln  Ser Thr Pro Tyr Val  Asn Ser Val Ala Val  Ser Ala Ser
    2000                 2005                 2010

Pro Thr  His Glu Asn Ser Val  Ser Ser Gly Ser Ser  Thr Ser Ser
    2015                 2020                 2025

Pro Tyr  Ser Ser Ala Ser Leu  Glu Ser Leu Asp Ser  Thr Ile Ser
    2030                 2035                 2040

Arg Arg  Asn Ala Ile Thr Ser  Trp Leu Trp Asp Leu  Thr Thr Ser
    2045                 2050                 2055

Leu Pro  Thr Thr Thr Trp Pro  Ser Thr Ser Leu Ser  Glu Ala Leu
    2060                 2065                 2070

Ser Ser  Gly His Ser Gly Val  Ser Asn Pro Ser Ser  Thr Thr Thr
    2075                 2080                 2085

Glu Phe  Pro Leu Phe Ser Ala  Ala Ser Thr Ser Ala  Ala Lys Gln
    2090                 2095                 2100

Arg Asn  Pro Glu Thr Glu Thr  His Gly Pro Gln Asn  Thr Ala Ala
    2105                 2110                 2115

Ser Thr  Leu Asn Thr Asp Ala  Ser Ser Val Thr Gly  Leu Ser Glu
    2120                 2125                 2130

Thr Pro  Val Gly Ala Ser Ile  Ser Ser Glu Val Pro  Leu Pro Met
    2135                 2140                 2145

Ala Ile  Thr Ser Arg Ser Asp  Val Ser Gly Leu Thr  Ser Glu Ser
    2150                 2155                 2160

Thr Ala  Asn Pro Ser Leu Gly  Thr Ala Ser Ser Ala  Gly Thr Lys
    2165                 2170                 2175

Leu Thr  Arg Thr Ile Ser Leu  Pro Thr Ser Glu Ser  Leu Val Ser
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    2180                2185                2190

Phe Arg  Met Asn Lys Asp Pro  Trp Thr Val Ser Ile  Pro Leu Gly
    2195                2200                2205

Ser His  Pro Thr Thr Asn Thr  Glu Thr Ser Ile Pro  Val Asn Ser
    2210                2215                2220

Ala Gly  Pro Pro Gly Leu Ser  Thr Val Ala Ser Asp  Val Ile Asp
    2225                2230                2235

Thr Pro  Ser Asp Gly Ala Glu  Ser Ile Pro Thr Val  Ser Phe Ser
    2240                2245                2250

Pro Ser  Pro Asp Thr Glu Val  Thr Thr Ile Ser His  Phe Pro Glu
    2255                2260                2265

Lys Thr  Thr His Ser Phe Arg  Thr Ile Ser Ser Leu  Thr His Glu
    2270                2275                2280

Leu Thr  Ser Arg Val Thr Pro  Ile Pro Gly Asp Trp  Met Ser Ser
    2285                2290                2295

Ala Met  Ser Thr Lys Pro Thr  Gly Ala Ser Pro Ser  Ile Thr Leu
    2300                2305                2310

Gly Glu  Arg Arg Thr Ile Thr  Ser Ala Ala Pro Thr  Thr Ser Pro
    2315                2320                2325

Ile Val  Leu Thr Ala Ser Phe  Thr Glu Thr Ser Thr  Val Ser Leu
    2330                2335                2340

Asp Asn  Glu Thr Thr Val Lys  Thr Ser Asp Ile Leu  Asp Ala Arg
    2345                2350                2355

Lys Thr  Asn Glu Leu Pro Ser  Asp Ser Ser Ser Ser  Ser Asp Leu
    2360                2365                2370

Ile Asn  Thr Ser Ile Ala Ser  Ser Thr Met Asp Val  Thr Lys Thr
    2375                2380                2385

Ala Ser  Ile Ser Pro Thr Ser  Ile Ser Gly Met Thr  Ala Ser Ser
    2390                2395                2400

Ser Pro  Ser Leu Phe Ser Ser  Asp Arg Pro Gln Val  Pro Thr Ser
    2405                2410                2415

Thr Thr  Glu Thr Asn Thr Ala  Thr Ser Pro Ser Val  Ser Ser Asn
    2420                2425                2430

Thr Tyr  Ser Leu Asp Gly Gly  Ser Asn Val Gly Gly  Thr Pro Ser
    2435                2440                2445

Thr Leu  Pro Pro Phe Thr Ile  Thr His Pro Val Glu  Thr Ser Ser
    2450                2455                2460

Ala Leu  Leu Ala Trp Ser Arg  Pro Val Arg Thr Phe  Ser Thr Met
    2465                2470                2475

Val Ser  Thr Asp Thr Ala Ser  Gly Glu Asn Pro Thr  Ser Ser Asn
    2480                2485                2490

Ser Val  Val Thr Ser Val Pro  Ala Pro Gly Thr Trp  Thr Ser Val
    2495                2500                2505

Gly Ser  Thr Thr Asp Leu Pro  Ala Met Gly Phe Leu  Lys Thr Ser
    2510                2515                2520

Pro Ala  Gly Glu Ala His Ser  Leu Leu Ala Ser Thr  Ile Glu Pro
    2525                2530                2535

Ala Thr  Ala Phe Thr Pro His  Leu Ser Ala Ala Val  Val Thr Gly
    2540                2545                2550

Ser Ser  Ala Thr Ser Glu Ala  Ser Leu Leu Thr Thr  Ser Glu Ser
    2555                2560                2565

Lys Ala  Ile His Ser Ser Pro  Gln Thr Pro Thr Thr  Pro Thr Ser
    2570                2575                2580
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Gly Ala  Asn Trp Glu Thr Ser  Ala Thr Pro Glu Ser  Leu Leu Val
    2585                 2590                 2595

Val Thr  Glu Thr Ser Asp Thr  Thr Leu Thr Ser Lys  Ile Leu Val
    2600                 2605                 2610

Thr Asp  Thr Ile Leu Phe Ser  Thr Val Ser Thr Pro  Pro Ser Lys
    2615                 2620                 2625

Phe Pro  Ser Thr Gly Thr Leu  Ser Gly Ala Ser Phe  Pro Thr Leu
    2630                 2635                 2640

Leu Pro  Asp Thr Pro Ala Ile  Pro Leu Thr Ala Thr  Glu Pro Thr
    2645                 2650                 2655

Ser Ser  Leu Ala Thr Ser Phe  Asp Ser Thr Pro Leu  Val Thr Ile
    2660                 2665                 2670

Ala Ser  Asp Ser Leu Gly Thr  Val Pro Glu Thr Thr  Leu Thr Met
    2675                 2680                 2685

Ser Glu  Thr Ser Asn Gly Asp  Ala Leu Val Leu Lys  Thr Val Ser
    2690                 2695                 2700

Asn Pro  Asp Arg Ser Ile Pro  Gly Ile Thr Ile Gln  Gly Val Thr
    2705                 2710                 2715

Glu Ser  Pro Leu His Pro Ser  Ser Thr Ser Pro Ser  Lys Ile Val
    2720                 2725                 2730

Ala Pro  Arg Asn Thr Thr Tyr  Glu Gly Ser Ile Thr  Val Ala Leu
    2735                 2740                 2745

Ser Thr  Leu Pro Ala Gly Thr  Thr Gly Ser Leu Val  Phe Ser Gln
    2750                 2755                 2760

Ser Ser  Glu Asn Ser Glu Thr  Thr Ala Leu Val Asp  Ser Ser Ala
    2765                 2770                 2775

Gly Leu  Glu Arg Ala Ser Val  Met Pro Leu Thr Thr  Gly Ser Gln
    2780                 2785                 2790

Gly Met  Ala Ser Ser Gly Gly  Ile Arg Ser Gly Ser  Thr His Ser
    2795                 2800                 2805

Thr Gly  Thr Lys Thr Phe Ser  Ser Leu Pro Leu Thr  Met Asn Pro
    2810                 2815                 2820

Gly Glu  Val Thr Ala Met Ser  Glu Ile Thr Thr Asn  Arg Leu Thr
    2825                 2830                 2835

Ala Thr  Gln Ser Thr Ala Pro  Lys Gly Ile Pro Val  Lys Pro Thr
    2840                 2845                 2850

Ser Ala  Glu Ser Gly Leu Leu  Thr Pro Val Ser Ala  Ser Ser Ser
    2855                 2860                 2865

Pro Ser  Lys Ala Phe Ala Ser  Leu Thr Thr Ala Pro  Pro Thr Trp
    2870                 2875                 2880

Gly Ile  Pro Gln Ser Thr Leu  Thr Phe Glu Phe Ser  Glu Val Pro
    2885                 2890                 2895

Ser Leu  Asp Thr Lys Ser Ala  Ser Leu Pro Thr Pro  Gly Gln Ser
    2900                 2905                 2910

Leu Asn  Thr Ile Pro Asp Ser  Asp Ala Ser Thr Ala  Ser Ser Ser
    2915                 2920                 2925

Leu Ser  Lys Ser Pro Glu Lys  Asn Pro Arg Ala Arg  Met Met Thr
    2930                 2935                 2940

Ser Thr  Lys Ala Ile Ser Ala  Ser Ser Phe Gln Ser  Thr Gly Phe
    2945                 2950                 2955

Thr Glu  Thr Pro Glu Gly Ser  Ala Ser Pro Ser Met  Ala Gly His
    2960                 2965                 2970
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Glu Pro  Arg Val Pro Thr Ser  Gly Thr Gly Asp Pro  Arg Tyr Ala
    2975                 2980                 2985

Ser Glu  Ser Met Ser Tyr Pro  Asp Pro Ser Lys Ala  Ser Ser Ala
    2990                 2995                 3000

Met Thr  Ser Thr Ser Leu Ala  Ser Lys Leu Thr Thr  Leu Phe Ser
    3005                 3010                 3015

Thr Gly  Gln Ala Ala Arg Ser  Gly Ser Ser Ser Ser  Pro Ile Ser
    3020                 3025                 3030

Leu Ser  Thr Glu Lys Glu Thr  Ser Phe Leu Ser Pro  Thr Ala Ser
    3035                 3040                 3045

Thr Ser  Arg Lys Thr Ser Leu  Phe Leu Gly Pro Ser  Met Ala Arg
    3050                 3055                 3060

Gln Pro  Asn Ile Leu Val His  Leu Gln Thr Ser Ala  Leu Thr Leu
    3065                 3070                 3075

Ser Pro  Thr Ser Thr Leu Asn  Met Ser Gln Glu Glu  Pro Pro Glu
    3080                 3085                 3090

Leu Thr  Ser Ser Gln Thr Ile  Ala Glu Glu Glu Gly  Thr Thr Ala
    3095                 3100                 3105

Glu Thr  Gln Thr Leu Thr Phe  Thr Pro Ser Glu Thr  Pro Thr Ser
    3110                 3115                 3120

Leu Leu  Pro Val Ser Ser Pro  Thr Glu Pro Thr Ala  Arg Arg Lys
    3125                 3130                 3135

Ser Ser  Pro Glu Thr Trp Ala  Ser Ser Ile Ser Val  Pro Ala Lys
    3140                 3145                 3150

Thr Ser  Leu Val Glu Thr Thr  Asp Gly Thr Leu Val  Thr Thr Ile
    3155                 3160                 3165

Lys Met  Ser Ser Gln Ala Ala  Gln Gly Asn Ser Thr  Trp Pro Ala
    3170                 3175                 3180

Pro Ala  Glu Glu Thr Gly Ser  Ser Pro Ala Gly Thr  Ser Pro Gly
    3185                 3190                 3195

Ser Pro  Glu Met Ser Thr Thr  Leu Lys Ile Met Ser  Ser Lys Glu
    3200                 3205                 3210

Pro Ser  Ile Ser Pro Glu Ile  Arg Ser Thr Val Arg  Asn Ser Pro
    3215                 3220                 3225

Trp Lys  Thr Pro Glu Thr Thr  Val Pro Met Glu Thr  Thr Val Glu
    3230                 3235                 3240

Pro Val  Thr Leu Gln Ser Thr  Ala Leu Gly Ser Gly  Ser Thr Ser
    3245                 3250                 3255

Ile Ser  His Leu Pro Thr Gly  Thr Thr Ser Pro Thr  Lys Ser Pro
    3260                 3265                 3270

Thr Glu  Asn Met Leu Ala Thr  Glu Arg Val Ser Leu  Ser Pro Ser
    3275                 3280                 3285

Pro Pro  Glu Ala Trp Thr Asn  Leu Tyr Ser Gly Thr  Pro Gly Gly
    3290                 3295                 3300

Thr Arg  Gln Ser Leu Ala Thr  Met Ser Ser Val Ser  Leu Glu Ser
    3305                 3310                 3315

Pro Thr  Ala Arg Ser Ile Thr  Gly Thr Gly Gln Gln  Ser Ser Pro
    3320                 3325                 3330

Glu Leu  Val Ser Lys Thr Thr  Gly Met Glu Phe Ser  Met Trp His
    3335                 3340                 3345

Gly Ser  Thr Gly Gly Thr Thr  Gly Asp Thr His Val  Ser Leu Ser
    3350                 3355                 3360

Thr Ser  Ser Asn Ile Leu Glu  Asp Pro Val Thr Ser  Pro Asn Ser
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    3365                3370                3375

Val Ser  Ser Leu Thr Asp Lys  Ser Lys His Lys Thr  Glu Thr Trp
    3380                3385                3390

Val Ser  Thr Thr Ala Ile Pro  Ser Thr Val Leu Asn  Asn Lys Ile
    3395                3400                3405

Met Ala  Ala Glu Gln Gln Thr  Ser Arg Ser Val Asp  Glu Ala Tyr
    3410                3415                3420

Ser Ser  Thr Ser Ser Trp Ser  Asp Gln Thr Ser Gly  Ser Asp Ile
    3425                3430                3435

Thr Leu  Gly Ala Ser Pro Asp  Val Thr Asn Thr Leu  Tyr Ile Thr
    3440                3445                3450

Ser Thr  Ala Gln Thr Thr Ser  Leu Val Ser Leu Pro  Ser Gly Asp
    3455                3460                3465

Gln Gly  Ile Thr Ser Leu Thr  Asn Pro Ser Gly Gly  Lys Thr Ser
    3470                3475                3480

Ser Ala  Ser Ser Val Thr Ser  Pro Ser Ile Gly Leu  Glu Thr Leu
    3485                3490                3495

Arg Ala  Asn Val Ser Ala Val  Lys Ser Asp Ile Ala  Pro Thr Ala
    3500                3505                3510

Gly His  Leu Ser Gln Thr Ser  Ser Pro Ala Glu Val  Ser Ile Leu
    3515                3520                3525

Asp Val  Thr Thr Ala Pro Thr  Pro Gly Ile Ser Thr  Thr Ile Thr
    3530                3535                3540

Thr Met  Gly Thr Asn Ser Ile  Ser Thr Thr Thr Pro  Asn Pro Glu
    3545                3550                3555

Val Gly  Met Ser Thr Met Asp  Ser Thr Pro Ala Thr  Glu Arg Arg
    3560                3565                3570

Thr Thr  Ser Thr Glu His Pro  Ser Thr Trp Ser Ser  Thr Ala Ala
    3575                3580                3585

Ser Asp  Ser Trp Thr Val Thr  Asp Met Thr Ser Asn  Leu Lys Val
    3590                3595                3600

Ala Arg  Ser Pro Gly Thr Ile  Ser Thr Met His Thr  Thr Ser Phe
    3605                3610                3615

Leu Ala  Ser Ser Thr Glu Leu  Asp Ser Met Ser Thr  Pro His Gly
    3620                3625                3630

Arg Ile  Thr Val Ile Gly Thr  Ser Leu Val Thr Pro  Ser Ser Asp
    3635                3640                3645

Ala Ser  Ala Val Lys Thr Glu  Thr Ser Thr Ser Glu  Arg Thr Leu
    3650                3655                3660

Ser Pro  Ser Asp Thr Thr Ala  Ser Thr Pro Ile Ser  Thr Phe Ser
    3665                3670                3675

Arg Val  Gln Arg Met Ser Ile  Ser Val Pro Asp Ile  Leu Ser Thr
    3680                3685                3690

Ser Trp  Thr Pro Ser Ser Thr  Glu Ala Glu Asp Val  Pro Val Ser
    3695                3700                3705

Met Val  Ser Thr Asp His Ala  Ser Thr Lys Thr Asp  Pro Asn Thr
    3710                3715                3720

Pro Leu  Ser Thr Phe Leu Phe  Asp Ser Leu Ser Thr  Leu Asp Trp
    3725                3730                3735

Asp Thr  Gly Arg Ser Leu Ser  Ser Ala Thr Ala Thr  Thr Ser Ala
    3740                3745                3750

Pro Gln  Gly Ala Thr Thr Pro  Gln Glu Leu Thr Leu  Glu Thr Met
    3755                3760                3765
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Ile Ser  Pro Ala Thr Ser Gln  Leu Pro Phe Ser Ile  Gly His Ile
    3770                 3775                 3780

Thr Ser  Ala Val Thr Pro Ala  Ala Met Ala Arg Ser  Ser Gly Val
    3785                 3790                 3795

Thr Phe  Ser Arg Pro Asp Pro  Thr Ser Lys Lys Ala  Glu Gln Thr
    3800                 3805                 3810

Ser Thr  Gln Leu Pro Thr Thr  Thr Ser Ala His Pro  Gly Gln Val
    3815                 3820                 3825

Pro Arg  Ser Ala Ala Thr Thr  Leu Asp Val Ile Pro  His Thr Ala
    3830                 3835                 3840

Lys Thr  Pro Asp Ala Thr Phe  Gln Arg Gln Gly Gln  Thr Ala Leu
    3845                 3850                 3855

Thr Thr  Glu Ala Arg Ala Thr  Ser Asp Ser Trp Asn  Glu Lys Glu
    3860                 3865                 3870

Lys Ser  Thr Pro Ser Ala Pro  Trp Ile Thr Glu Met  Met Asn Ser
    3875                 3880                 3885

Val Ser  Glu Asp Thr Ile Lys  Glu Val Thr Ser Ser  Ser Ser Val
    3890                 3895                 3900

Leu Arg  Thr Leu Asn Thr Leu  Asp Ile Asn Leu Glu  Ser Gly Thr
    3905                 3910                 3915

Thr Ser  Ser Pro Ser Trp Lys  Ser Ser Pro Tyr Glu  Arg Ile Ala
    3920                 3925                 3930

Pro Ser  Glu Ser Thr Thr Asp  Lys Glu Ala Ile His  Pro Ser Thr
    3935                 3940                 3945

Asn Thr  Val Glu Thr Thr Gly  Trp Val Thr Ser Ser  Glu His Ala
    3950                 3955                 3960

Ser His  Ser Thr Ile Pro Ala  His Ser Ala Ser Ser  Lys Leu Thr
    3965                 3970                 3975

Ser Pro  Val Val Thr Thr Ser  Thr Arg Glu Gln Ala  Ile Val Ser
    3980                 3985                 3990

Met Ser  Thr Thr Thr Trp Pro  Glu Ser Thr Arg Ala  Arg Thr Glu
    3995                 4000                 4005

Pro Asn  Ser Phe Leu Thr Ile  Glu Leu Arg Asp Val  Ser Pro Tyr
    4010                 4015                 4020

Met Asp  Thr Ser Ser Thr Thr  Gln Thr Ser Ile Ile  Ser Ser Pro
    4025                 4030                 4035

Gly Ser  Thr Ala Ile Thr Lys  Gly Pro Arg Thr Glu  Ile Thr Ser
    4040                 4045                 4050

Ser Lys  Arg Ile Ser Ser Ser  Phe Leu Ala Gln Ser  Met Arg Ser
    4055                 4060                 4065

Ser Asp  Ser Pro Ser Glu Ala  Ile Thr Arg Leu Ser  Asn Phe Pro
    4070                 4075                 4080

Ala Met  Thr Glu Ser Gly Gly  Met Ile Leu Ala Met  Gln Thr Ser
    4085                 4090                 4095

Pro Pro  Gly Ala Thr Ser Leu  Ser Ala Pro Thr Leu  Asp Thr Ser
    4100                 4105                 4110

Ala Thr  Ala Ser Trp Thr Gly  Thr Pro Leu Ala Thr  Thr Gln Arg
    4115                 4120                 4125

Phe Thr  Tyr Ser Glu Lys Thr  Thr Leu Phe Ser Lys  Gly Pro Glu
    4130                 4135                 4140

Asp Thr  Ser Gln Pro Ser Pro  Pro Ser Val Glu Glu  Thr Ser Ser
    4145                 4150                 4155
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Ser Ser  Ser Leu Val Pro Ile  His Ala Thr Thr Ser  Pro Ser Asn
    4160                 4165                 4170

Ile Leu  Leu Thr Ser Gln Gly  His Ser Pro Ser Ser  Thr Pro Pro
    4175                 4180                 4185

Val Thr  Ser Val Phe Leu Ser  Glu Thr Ser Gly Leu  Gly Lys Thr
    4190                 4195                 4200

Thr Asp  Met Ser Arg Ile Ser  Leu Glu Pro Gly Thr  Ser Leu Pro
    4205                 4210                 4215

Pro Asn  Leu Ser Ser Thr Ala  Gly Glu Ala Leu Ser  Thr Tyr Glu
    4220                 4225                 4230

Ala Ser  Arg Asp Thr Lys Ala  Ile His His Ser Ala  Asp Thr Ala
    4235                 4240                 4245

Val Thr  Asn Met Glu Ala Thr  Ser Ser Glu Tyr Ser  Pro Ile Pro
    4250                 4255                 4260

Gly His  Thr Lys Pro Ser Lys  Ala Thr Ser Pro Leu  Val Thr Ser
    4265                 4270                 4275

His Ile  Met Gly Asp Ile Thr  Ser Ser Thr Ser Val  Phe Gly Ser
    4280                 4285                 4290

Ser Glu  Thr Thr Glu Ile Glu  Thr Val Ser Ser Val  Asn Gln Gly
    4295                 4300                 4305

Leu Gln  Glu Arg Ser Thr Ser  Gln Val Ala Ser Ser  Ala Thr Glu
    4310                 4315                 4320

Thr Ser  Thr Val Ile Thr His  Val Ser Ser Gly Asp  Ala Thr Thr
    4325                 4330                 4335

His Val  Thr Lys Thr Gln Ala  Thr Phe Ser Ser Gly  Thr Ser Ile
    4340                 4345                 4350

Ser Ser  Pro His Gln Phe Ile  Thr Ser Thr Asn Thr  Phe Thr Asp
    4355                 4360                 4365

Val Ser  Thr Asn Pro Ser Thr  Ser Leu Ile Met Thr  Glu Ser Ser
    4370                 4375                 4380

Gly Val  Thr Ile Thr Thr Gln  Thr Gly Pro Thr Gly  Ala Ala Thr
    4385                 4390                 4395

Gln Gly  Pro Tyr Leu Leu Asp  Thr Ser Thr Met Pro  Tyr Leu Thr
    4400                 4405                 4410

Glu Thr  Pro Leu Ala Val Thr  Pro Asp Phe Met Gln  Ser Glu Lys
    4415                 4420                 4425

Thr Thr  Leu Ile Ser Lys Gly  Pro Lys Asp Val Ser  Trp Thr Ser
    4430                 4435                 4440

Pro Pro  Ser Val Ala Glu Thr  Ser Tyr Pro Ser Ser  Leu Thr Pro
    4445                 4450                 4455

Phe Leu  Val Thr Thr Ile Pro  Pro Ala Thr Ser Thr  Leu Gln Gly
    4460                 4465                 4470

Gln His  Thr Ser Ser Pro Val  Ser Ala Thr Ser Val  Leu Thr Ser
    4475                 4480                 4485

Gly Leu  Val Lys Thr Thr Asp  Met Leu Asn Thr Ser  Met Glu Pro
    4490                 4495                 4500

Val Thr  Asn Ser Pro Gln Asn  Leu Asn Asn Pro Ser  Asn Glu Ile
    4505                 4510                 4515

Leu Ala  Thr Leu Ala Ala Thr  Thr Asp Ile Glu Thr  Ile His Pro
    4520                 4525                 4530

Ser Ile  Asn Lys Ala Val Thr  Asn Met Gly Thr Ala  Ser Ser Ala
    4535                 4540                 4545

His Val  Leu His Ser Thr Leu  Pro Val Ser Ser Glu  Pro Ser Thr
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    4550                4555                4560

Ala Thr  Ser Pro Met Val Pro  Ala Ser Ser Met Gly  Asp Ala Leu
    4565                4570                4575

Ala Ser  Ile Ser Ile Pro Gly  Ser Glu Thr Thr Asp  Ile Glu Gly
    4580                4585                4590

Glu Pro  Thr Ser Ser Leu Thr  Ala Gly Arg Lys Glu  Asn Ser Thr
    4595                4600                4605

Leu Gln  Glu Met Asn Ser Thr  Thr Glu Ser Asn Ile  Ile Leu Ser
    4610                4615                4620

Asn Val  Ser Val Gly Ala Ile  Thr Glu Ala Thr Lys  Met Glu Val
    4625                4630                4635

Pro Ser  Phe Asp Ala Thr Phe  Ile Pro Thr Pro Ala  Gln Ser Thr
    4640                4645                4650

Lys Phe  Pro Asp Ile Phe Ser  Val Ala Ser Ser Arg  Leu Ser Asn
    4655                4660                4665

Ser Pro  Pro Met Thr Ile Ser  Thr His Met Thr Thr  Thr Gln Thr
    4670                4675                4680

Gly Ser  Ser Gly Ala Thr Ser  Lys Ile Pro Leu Ala  Leu Asp Thr
    4685                4690                4695

Ser Thr  Leu Glu Thr Ser Ala  Gly Thr Pro Ser Val  Val Thr Glu
    4700                4705                4710

Gly Phe  Ala His Ser Lys Ile  Thr Thr Ala Met Asn  Asn Asp Val
    4715                4720                4725

Lys Asp  Val Ser Gln Thr Asn  Pro Pro Phe Gln Asp  Glu Ala Ser
    4730                4735                4740

Ser Pro  Ser Ser Gln Ala Pro  Val Leu Val Thr Thr  Leu Pro Ser
    4745                4750                4755

Ser Val  Ala Phe Thr Pro Gln  Trp His Ser Thr Ser  Ser Pro Val
    4760                4765                4770

Ser Met  Ser Ser Val Leu Thr  Ser Ser Leu Val Lys  Thr Ala Gly
    4775                4780                4785

Lys Val  Asp Thr Ser Leu Glu  Thr Val Thr Ser Ser  Pro Gln Ser
    4790                4795                4800

Met Ser  Asn Thr Leu Asp Asp  Ile Ser Val Thr Ser  Ala Ala Thr
    4805                4810                4815

Thr Asp  Ile Glu Thr Thr His  Pro Ser Ile Asn Thr  Val Val Thr
    4820                4825                4830

Asn Val  Gly Thr Thr Gly Ser  Ala Phe Glu Ser His  Ser Thr Val
    4835                4840                4845

Ser Ala  Tyr Pro Glu Pro Ser  Lys Val Thr Ser Pro  Asn Val Thr
    4850                4855                4860

Thr Ser  Thr Met Glu Asp Thr  Thr Ile Ser Arg Ser  Ile Pro Lys
    4865                4870                4875

Ser Ser  Lys Thr Thr Arg Thr  Glu Thr Glu Thr Thr  Ser Ser Leu
    4880                4885                4890

Thr Pro  Lys Leu Arg Glu Thr  Ser Ile Ser Gln Glu  Ile Thr Ser
    4895                4900                4905

Ser Thr  Glu Thr Ser Thr Val  Pro Tyr Lys Glu Leu  Thr Gly Ala
    4910                4915                4920

Thr Thr  Glu Val Ser Arg Thr  Asp Val Thr Ser Ser  Ser Ser Thr
    4925                4930                4935

Ser Phe  Pro Gly Pro Asp Gln  Ser Thr Val Ser Leu  Asp Ile Ser
    4940                4945                4950
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Thr Glu  Thr Asn Thr Arg Leu  Ser Thr Ser Pro Ile  Met Thr Glu
    4955                 4960                 4965

Ser Ala  Glu Ile Thr Ile Thr  Thr Gln Thr Gly Pro  His Gly Ala
    4970                 4975                 4980

Thr Ser  Gln Asp Thr Phe Thr  Met Asp Pro Ser Asn  Thr Thr Pro
    4985                 4990                 4995

Gln Ala  Gly Ile His Ser Ala  Met Thr His Gly Phe  Ser Gln Leu
    5000                 5005                 5010

Asp Val  Thr Thr Leu Met Ser  Arg Ile Pro Gln Asp  Val Ser Trp
    5015                 5020                 5025

Thr Ser  Pro Pro Ser Val Asp  Lys Thr Ser Ser Pro  Ser Ser Phe
    5030                 5035                 5040

Leu Ser  Ser Pro Ala Met Thr  Thr Pro Ser Leu Ile  Ser Ser Thr
    5045                 5050                 5055

Leu Pro  Glu Asp Lys Leu Ser  Ser Pro Met Thr Ser  Leu Leu Thr
    5060                 5065                 5070

Ser Gly  Leu Val Lys Ile Thr  Asp Ile Leu Arg Thr  Arg Leu Glu
    5075                 5080                 5085

Pro Val  Thr Ser Ser Leu Pro  Asn Phe Ser Ser Thr  Ser Asp Lys
    5090                 5095                 5100

Ile Leu  Ala Thr Ser Lys Asp  Ser Lys Asp Thr Lys  Glu Ile Phe
    5105                 5110                 5115

Pro Ser  Ile Asn Thr Glu Glu  Thr Asn Val Lys Ala  Asn Asn Ser
    5120                 5125                 5130

Gly His  Glu Ser His Ser Pro  Ala Leu Ala Asp Ser  Glu Thr Pro
    5135                 5140                 5145

Lys Ala  Thr Thr Gln Met Val  Ile Thr Thr Thr Val  Gly Asp Pro
    5150                 5155                 5160

Ala Pro  Ser Thr Ser Met Pro  Val His Gly Ser Ser  Glu Thr Thr
    5165                 5170                 5175

Asn Ile  Lys Arg Glu Pro Thr  Tyr Phe Leu Thr Pro  Arg Leu Arg
    5180                 5185                 5190

Glu Thr  Ser Thr Ser Gln Glu  Ser Ser Phe Pro Thr  Asp Thr Ser
    5195                 5200                 5205

Phe Leu  Leu Ser Lys Val Pro  Thr Gly Thr Ile Thr  Glu Val Ser
    5210                 5215                 5220

Ser Thr  Gly Val Asn Ser Ser  Ser Lys Ile Ser Thr  Pro Asp His
    5225                 5230                 5235

Asp Lys  Ser Thr Val Pro Pro  Asp Thr Phe Thr Gly  Glu Ile Pro
    5240                 5245                 5250

Arg Val  Phe Thr Ser Ser Ile  Lys Thr Lys Ser Ala  Glu Met Thr
    5255                 5260                 5265

Ile Thr  Thr Gln Ala Ser Pro  Pro Glu Ser Ala Ser  His Ser Thr
    5270                 5275                 5280

Leu Pro  Leu Asp Thr Ser Thr  Thr Leu Ser Gln Gly  Gly Thr His
    5285                 5290                 5295

Ser Thr  Val Thr Gln Gly Phe  Pro Tyr Ser Glu Val  Thr Thr Leu
    5300                 5305                 5310

Met Gly  Met Gly Pro Gly Asn  Val Ser Trp Met Thr  Thr Pro Pro
    5315                 5320                 5325

Val Glu  Glu Thr Ser Ser Val  Ser Ser Leu Met Ser  Ser Pro Ala
    5330                 5335                 5340
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Met Thr  Ser Pro Ser Pro Val  Ser Ser Thr Ser Pro  Gln Ser Ile
    5345                 5350                 5355

Pro Ser  Ser Pro Leu Pro Val  Thr Ala Leu Pro Thr  Ser Val Leu
    5360                 5365                 5370

Val Thr  Thr Thr Asp Val Leu  Gly Thr Thr Ser Pro  Glu Ser Val
    5375                 5380                 5385

Thr Ser  Ser Pro Pro Asn Leu  Ser Ser Ile Thr His  Glu Arg Pro
    5390                 5395                 5400

Ala Thr  Tyr Lys Asp Thr Ala  His Thr Glu Ala Ala  Met His His
    5405                 5410                 5415

Ser Thr  Asn Thr Ala Val Thr  Asn Val Gly Thr Ser  Gly Ser Gly
    5420                 5425                 5430

His Lys  Ser Gln Ser Ser Val  Leu Ala Asp Ser Glu  Thr Ser Lys
    5435                 5440                 5445

Ala Thr  Pro Leu Met Ser Thr  Thr Ser Thr Leu Gly  Asp Thr Ser
    5450                 5455                 5460

Val Ser  Thr Ser Thr Pro Asn  Ile Ser Gln Thr Asn  Gln Ile Gln
    5465                 5470                 5475

Thr Glu  Pro Thr Ala Ser Leu  Ser Pro Arg Leu Arg  Glu Ser Ser
    5480                 5485                 5490

Thr Ser  Glu Lys Thr Ser Ser  Thr Thr Glu Thr Asn  Thr Ala Phe
    5495                 5500                 5505

Ser Tyr  Val Pro Thr Gly Ala  Ile Thr Gln Ala Ser  Arg Thr Glu
    5510                 5515                 5520

Ile Ser  Ser Ser Arg Thr Ser  Ile Ser Asp Leu Asp  Arg Pro Thr
    5525                 5530                 5535

Ile Ala  Pro Asp Ile Ser Thr  Gly Met Ile Thr Arg  Leu Phe Thr
    5540                 5545                 5550

Ser Pro  Ile Met Thr Lys Ser  Ala Glu Met Thr Val  Thr Thr Gln
    5555                 5560                 5565

Thr Thr  Thr Pro Gly Ala Thr  Ser Gln Gly Ile Leu  Pro Trp Asp
    5570                 5575                 5580

Thr Ser  Thr Thr Leu Phe Gln  Gly Gly Thr His Ser  Thr Val Ser
    5585                 5590                 5595

Gln Gly  Phe Pro His Ser Glu  Ile Thr Thr Leu Arg  Ser Arg Thr
    5600                 5605                 5610

Pro Gly  Asp Val Ser Trp Met  Thr Thr Pro Pro Val  Glu Glu Thr
    5615                 5620                 5625

Ser Ser  Gly Phe Ser Leu Met  Ser Pro Ser Met Thr  Ser Pro Ser
    5630                 5635                 5640

Pro Val  Ser Ser Thr Ser Pro  Glu Ser Ile Pro Ser  Ser Pro Leu
    5645                 5650                 5655

Pro Val  Thr Ala Leu Leu Thr  Ser Val Leu Val Thr  Thr Thr Asn
    5660                 5665                 5670

Val Leu  Gly Thr Thr Ser Pro  Glu Pro Val Thr Ser  Ser Pro Pro
    5675                 5680                 5685

Asn Leu  Ser Ser Pro Thr Gln  Glu Arg Leu Thr Thr  Tyr Lys Asp
    5690                 5695                 5700

Thr Ala  His Thr Glu Ala Met  His Ala Ser Met His  Thr Asn Thr
    5705                 5710                 5715

Ala Val  Ala Asn Val Gly Thr  Ser Ile Ser Gly His  Glu Ser Gln
    5720                 5725                 5730

Ser Ser  Val Pro Ala Asp Ser  His Thr Ser Lys Ala  Thr Ser Pro
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    5735                5740                5745

Met Gly  Ile Thr Phe Ala Met  Gly Asp Thr Ser Val  Ser Thr Ser
    5750                5755                5760

Thr Pro  Ala Phe Phe Glu Thr  Arg Ile Gln Thr Glu  Ser Thr Ser
    5765                5770                5775

Ser Leu  Ile Pro Gly Leu Arg  Asp Thr Arg Thr Ser  Glu Glu Ile
    5780                5785                5790

Asn Thr  Val Thr Glu Thr Ser  Thr Val Leu Ser Glu  Val Pro Thr
    5795                5800                5805

Thr Thr  Thr Thr Glu Val Ser  Arg Thr Glu Val Ile  Thr Ser Ser
    5810                5815                5820

Arg Thr  Thr Ile Ser Gly Pro  Asp His Ser Lys Met  Ser Pro Tyr
    5825                5830                5835

Ile Ser  Thr Glu Thr Ile Thr  Arg Leu Ser Thr Phe  Pro Phe Val
    5840                5845                5850

Thr Gly  Ser Thr Glu Met Ala  Ile Thr Asn Gln Thr  Gly Pro Ile
    5855                5860                5865

Gly Thr  Ile Ser Gln Ala Thr  Leu Thr Leu Asp Thr  Ser Ser Thr
    5870                5875                5880

Ala Ser  Trp Glu Gly Thr His  Ser Pro Val Thr Gln  Arg Phe Pro
    5885                5890                5895

His Ser  Glu Glu Thr Thr Thr  Met Ser Arg Ser Thr  Lys Gly Val
    5900                5905                5910

Ser Trp  Gln Ser Pro Pro Ser  Val Glu Glu Thr Ser  Ser Pro Ser
    5915                5920                5925

Ser Pro  Val Pro Leu Pro Ala  Ile Thr Ser His Ser  Ser Leu Tyr
    5930                5935                5940

Ser Ala  Val Ser Gly Ser Ser  Pro Thr Ser Ala Leu  Pro Val Thr
    5945                5950                5955

Ser Leu  Leu Thr Ser Gly Arg  Arg Lys Thr Ile Asp  Met Leu Asp
    5960                5965                5970

Thr His  Ser Glu Leu Val Thr  Ser Ser Leu Pro Ser  Ala Ser Ser
    5975                5980                5985

Phe Ser  Gly Glu Ile Leu Thr  Ser Glu Ala Ser Thr  Asn Thr Glu
    5990                5995                6000

Thr Ile  His Phe Ser Glu Asn  Thr Ala Glu Thr Asn  Met Gly Thr
    6005                6010                6015

Thr Asn  Ser Met His Lys Leu  His Ser Ser Val Ser  Ile His Ser
    6020                6025                6030

Gln Pro  Ser Gly His Thr Pro  Pro Lys Val Thr Gly  Ser Met Met
    6035                6040                6045

Glu Asp  Ala Ile Val Ser Thr  Ser Thr Pro Gly Ser  Pro Glu Thr
    6050                6055                6060

Lys Asn  Val Asp Arg Asp Ser  Thr Ser Pro Leu Thr  Pro Glu Leu
    6065                6070                6075

Lys Glu  Asp Ser Thr Ala Leu  Val Met Asn Ser Thr  Thr Glu Ser
    6080                6085                6090

Asn Thr  Val Phe Ser Ser Val  Ser Leu Asp Ala Ala  Thr Glu Val
    6095                6100                6105

Ser Arg  Ala Glu Val Thr Tyr  Tyr Asp Pro Thr Phe  Met Pro Ala
    6110                6115                6120

Ser Ala  Gln Ser Thr Lys Ser  Pro Asp Ile Ser Pro  Glu Ala Ser
    6125                6130                6135
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Ser Ser  His Ser Asn Ser Pro  Pro Leu Thr Ile Ser  Thr His Lys
    6140                 6145                 6150

Thr Ile  Ala Thr Gln Thr Gly  Pro Ser Gly Val Thr  Ser Leu Gly
    6155                 6160                 6165

Gln Leu  Thr Leu Asp Thr Ser  Thr Ile Ala Thr Ser  Ala Gly Thr
    6170                 6175                 6180

Pro Ser  Ala Arg Thr Gln Asp  Phe Val Asp Ser Glu  Thr Thr Ser
    6185                 6190                 6195

Val Met  Asn Asn Asp Leu Asn  Asp Val Leu Lys Thr  Ser Pro Phe
    6200                 6205                 6210

Ser Ala  Glu Glu Ala Asn Ser  Leu Ser Ser Gln Ala  Pro Leu Leu
    6215                 6220                 6225

Val Thr  Thr Ser Pro Ser Pro  Val Thr Ser Thr Leu  Gln Glu His
    6230                 6235                 6240

Ser Thr  Ser Ser Leu Val Ser  Val Thr Ser Val Pro  Thr Pro Thr
    6245                 6250                 6255

Leu Ala  Lys Ile Thr Asp Met  Asp Thr Asn Leu Glu  Pro Val Thr
    6260                 6265                 6270

Arg Ser  Pro Gln Asn Leu Arg  Asn Thr Leu Ala Thr  Ser Glu Ala
    6275                 6280                 6285

Thr Thr  Asp Thr His Thr Met  His Pro Ser Ile Asn  Thr Ala Val
    6290                 6295                 6300

Ala Asn  Val Gly Thr Thr Ser  Ser Pro Asn Glu Phe  Tyr Phe Thr
    6305                 6310                 6315

Val Ser  Pro Asp Ser Asp Pro  Tyr Lys Ala Thr Ser  Ala Val Val
    6320                 6325                 6330

Ile Thr  Ser Thr Ser Gly Asp  Ser Ile Val Ser Thr  Ser Met Pro
    6335                 6340                 6345

Arg Ser  Ser Ala Met Lys Lys  Ile Glu Ser Glu Thr  Thr Phe Ser
    6350                 6355                 6360

Leu Ile  Phe Arg Leu Arg Glu  Thr Ser Thr Ser Gln  Lys Ile Gly
    6365                 6370                 6375

Ser Ser  Ser Asp Thr Ser Thr  Val Phe Asp Lys Ala  Phe Thr Ala
    6380                 6385                 6390

Ala Thr  Thr Glu Val Ser Arg  Thr Glu Leu Thr Ser  Ser Ser Arg
    6395                 6400                 6405

Thr Ser  Ile Gln Gly Thr Glu  Lys Pro Thr Met Ser  Pro Asp Thr
    6410                 6415                 6420

Ser Thr  Arg Ser Val Thr Met  Leu Ser Thr Phe Ala  Gly Leu Thr
    6425                 6430                 6435

Lys Ser  Glu Glu Arg Thr Ile  Ala Thr Gln Thr Gly  Pro His Arg
    6440                 6445                 6450

Ala Thr  Ser Gln Gly Thr Leu  Thr Trp Asp Thr Ser  Ile Thr Thr
    6455                 6460                 6465

Ser Gln  Ala Gly Thr His Ser  Ala Met Thr His Gly  Phe Ser Gln
    6470                 6475                 6480

Leu Asp  Leu Ser Thr Leu Thr  Ser Arg Val Pro Glu  Tyr Ile Ser
    6485                 6490                 6495

Gly Thr  Ser Pro Pro Ser Val  Glu Lys Thr Ser Ser  Ser Ser Ser
    6500                 6505                 6510

Leu Leu  Ser Leu Pro Ala Ile  Thr Ser Pro Ser Pro  Val Pro Thr
    6515                 6520                 6525
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Thr Leu Pro Glu Ser Arg Pro Ser Ser Pro Val His Leu Thr Ser
6530 6535 6540

Leu Pro Thr Ser Gly Leu Val Lys Thr Thr Asp Met Leu Ala Ser
6545 6550 6555

Val Ala Ser Leu Pro Pro Asn Leu Gly Ser Thr Ser His Lys Ile
6560 6565 6570

Pro Thr Thr Ser Glu Asp Ile Lys Asp Thr Glu Lys Met Tyr Pro
6575 6580 6585

Ser Thr Asn Ile Ala Val Thr Asn Val Gly Thr Thr Thr Ser Glu
6590 6595 6600

Lys Glu Ser Tyr Ser Ser Val Pro Ala Tyr Ser Glu Pro Pro Lys
6605 6610 6615

Val Thr Ser Pro Met Val Thr Ser Phe Asn Ile Arg Asp Thr Ile
6620 6625 6630

Val Ser Thr Ser Met Pro Gly Ser Ser Glu Ile Thr Arg Ile Glu
6635 6640 6645

Met Glu Ser Thr Phe Ser Leu Ala His Gly Leu Lys Gly Thr Ser
6650 6655 6660

Thr Ser Gln Asp Pro Ile Val Ser Thr Glu Lys Ser Ala Val Leu
6665 6670 6675

His Lys Leu Thr Thr Gly Ala Thr Glu Thr Ser Arg Thr Glu Val
6680 6685 6690

Ala Ser Ser Arg Arg Thr Ser Ile Pro Gly Pro Asp His Ser Thr
6695 6700 6705

Glu Ser Pro Asp Ile Ser Thr Glu Val Ile Pro Ser Leu Pro Ile
6710 6715 6720

Ser Leu Gly Ile Thr Glu Ser Ser Asn Met Thr Ile Ile Thr Arg
6725 6730 6735

Thr Gly Pro Pro Leu Gly Ser Thr Ser Gln Gly Thr Phe Thr Leu
6740 6745 6750

Asp Thr Pro Thr Thr Ser Ser Arg Ala Gly Thr His Ser Met Ala
6755 6760 6765

Thr Gln Glu Phe Pro His Ser Glu Met Thr Thr Val Met Asn Lys
6770 6775 6780

Asp Pro Glu Ile Leu Ser Trp Thr Ile Pro Pro Ser Ile Glu Lys
6785 6790 6795

Thr Ser Phe Ser Ser Ser Leu Met Pro Ser Pro Ala Met Thr Ser
6800 6805 6810

Pro Pro Val Ser Ser Thr Leu Pro Lys Thr Ile His Thr Thr Pro
6815 6820 6825

Ser Pro Met Thr Ser Leu Leu Thr Pro Ser Leu Val Met Thr Thr
6830 6835 6840

Asp Thr Leu Gly Thr Ser Pro Glu Pro Thr Thr Ser Ser Pro Pro
6845 6850 6855

Asn Leu Ser Ser Thr Ser His Glu Ile Leu Thr Thr Asp Glu Asp
6860 6865 6870

Thr Thr Ala Ile Glu Ala Met His Pro Ser Thr Ser Thr Ala Ala
6875 6880 6885

Thr Asn Val Glu Thr Thr Ser Ser Gly His Gly Ser Gln Ser Ser
6890 6895 6900

Val Leu Ala Asp Ser Glu Lys Thr Lys Ala Thr Ala Pro Met Asp
6905 6910 6915

Thr Thr Ser Thr Met Gly His Thr Thr Val Ser Thr Ser Met Ser

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    6920                6925                6930

Val Ser  Ser Glu Thr Thr Lys  Ile Lys Arg Glu Ser  Thr Tyr Ser
    6935                6940                6945

Leu Thr  Pro Gly Leu Arg Glu  Thr Ser Ile Ser Gln  Asn Ala Ser
    6950                6955                6960

Phe Ser  Thr Asp Thr Ser Ile  Val Leu Ser Glu Val  Pro Thr Gly
    6965                6970                6975

Thr Thr  Ala Glu Val Ser Arg  Thr Glu Val Thr Ser  Ser Gly Arg
    6980                6985                6990

Thr Ser  Ile Pro Gly Pro Ser  Gln Ser Thr Val Leu  Pro Glu Ile
    6995                7000                7005

Ser Thr  Arg Thr Met Thr Arg  Leu Phe Ala Ser Pro  Thr Met Thr
    7010                7015                7020

Glu Ser  Ala Glu Met Thr Ile  Pro Thr Gln Thr Gly  Pro Ser Gly
    7025                7030                7035

Ser Thr  Ser Gln Asp Thr Leu  Thr Leu Asp Thr Ser  Thr Thr Lys
    7040                7045                7050

Ser Gln  Ala Lys Thr His Ser  Thr Leu Thr Gln Arg  Phe Pro His
    7055                7060                7065

Ser Glu  Met Thr Thr Leu Met  Ser Arg Gly Pro Gly  Asp Met Ser
    7070                7075                7080

Trp Gln  Ser Ser Pro Ser Leu  Glu Asn Pro Ser Ser  Leu Pro Ser
    7085                7090                7095

Leu Leu  Ser Leu Pro Ala Thr  Thr Ser Pro Pro Pro  Ile Ser Ser
    7100                7105                7110

Thr Leu  Pro Val Thr Ile Ser  Ser Ser Pro Leu Pro  Val Thr Ser
    7115                7120                7125

Leu Leu  Thr Ser Ser Pro Val  Thr Thr Thr Asp Met  Leu His Thr
    7130                7135                7140

Ser Pro  Glu Leu Val Thr Ser  Ser Pro Pro Lys Leu  Ser His Thr
    7145                7150                7155

Ser Asp  Glu Arg Leu Thr Thr  Gly Lys Asp Thr Thr  Asn Thr Glu
    7160                7165                7170

Ala Val  His Pro Ser Thr Asn  Thr Ala Ala Ser Asn  Val Glu Ile
    7175                7180                7185

Pro Ser  Ser Gly His Glu Ser  Pro Ser Ser Ala Leu  Ala Asp Ser
    7190                7195                7200

Glu Thr  Ser Lys Ala Thr Ser  Pro Met Phe Ile Thr  Ser Thr Gln
    7205                7210                7215

Glu Asp  Thr Thr Val Ala Ile  Ser Thr Pro His Phe  Leu Glu Thr
    7220                7225                7230

Ser Arg  Ile Gln Lys Glu Ser  Ile Ser Ser Leu Ser  Pro Lys Leu
    7235                7240                7245

Arg Glu  Thr Gly Ser Ser Val  Glu Thr Ser Ser Ala  Ile Glu Thr
    7250                7255                7260

Ser Ala  Val Leu Ser Glu Val  Ser Ile Gly Ala Thr  Thr Glu Ile
    7265                7270                7275

Ser Arg  Thr Glu Val Thr Ser  Ser Ser Arg Thr Ser  Ile Ser Gly
    7280                7285                7290

Ser Ala  Glu Ser Thr Met Leu  Pro Glu Ile Ser Thr  Thr Arg Lys
    7295                7300                7305

Ile Ile  Lys Phe Pro Thr Ser  Pro Ile Leu Ala Glu  Ser Ser Glu
    7310                7315                7320
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Met Thr Ile Lys Thr Gln Thr Ser Pro Pro Gly Ser Thr Ser Glu
7325 7330 7335

Ser Thr Phe Thr Leu Asp Thr Ser Thr Thr Pro Ser Leu Val Ile
7340 7345 7350

Thr His Ser Thr Met Thr Gln Arg Leu Pro His Ser Glu Ile Thr
7355 7360 7365

Thr Leu Val Ser Arg Gly Ala Gly Asp Val Pro Arg Pro Ser Ser
7370 7375 7380

Leu Pro Val Glu Glu Thr Ser Pro Pro Ser Ser Gln Leu Ser Leu
7385 7390 7395

Ser Ala Met Ile Ser Pro Ser Pro Val Ser Ser Thr Leu Pro Ala
7400 7405 7410

Ser Ser His Ser Ser Ser Ala Ser Val Thr Ser Leu Leu Thr Pro
7415 7420 7425

Gly Gln Val Lys Thr Thr Glu Val Leu Asp Ala Ser Ala Glu Pro
7430 7435 7440

Glu Thr Ser Ser Pro Pro Ser Leu Ser Ser Thr Ser Val Glu Ile
7445 7450 7455

Leu Ala Thr Ser Glu Val Thr Thr Asp Thr Glu Lys Ile His Pro
7460 7465 7470

Phe Ser Asn Thr Ala Val Thr Lys Val Gly Thr Ser Ser Ser Gly
7475 7480 7485

His Glu Ser Pro Ser Ser Val Leu Pro Asp Ser Glu Thr Thr Lys
7490 7495 7500

Ala Thr Ser Ala Met Gly Thr Ile Ser Ile Met Gly Asp Thr Ser
7505 7510 7515

Val Ser Thr Leu Thr Pro Ala Leu Ser Asn Thr Arg Lys Ile Gln
7520 7525 7530

Ser Glu Pro Ala Ser Ser Leu Thr Thr Arg Leu Arg Glu Thr Ser
7535 7540 7545

Thr Ser Glu Glu Thr Ser Leu Ala Thr Glu Ala Asn Thr Val Leu
7550 7555 7560

Ser Lys Val Ser Thr Gly Ala Thr Thr Glu Val Ser Arg Thr Glu
7565 7570 7575

Ala Ile Ser Phe Ser Arg Thr Ser Met Ser Gly Pro Glu Gln Ser
7580 7585 7590

Thr Met Ser Gln Asp Ile Ser Ile Gly Thr Ile Pro Arg Ile Ser
7595 7600 7605

Ala Ser Ser Val Leu Thr Glu Ser Ala Lys Met Thr Ile Thr Thr
7610 7615 7620

Gln Thr Gly Pro Ser Glu Ser Thr Leu Glu Ser Thr Leu Asn Leu
7625 7630 7635

Asn Thr Ala Thr Thr Pro Ser Trp Val Glu Thr His Ser Ile Val
7640 7645 7650

Ile Gln Gly Phe Pro His Pro Glu Met Thr Thr Ser Met Gly Arg
7655 7660 7665

Gly Pro Gly Gly Val Ser Trp Pro Ser Pro Pro Phe Val Lys Glu
7670 7675 7680

Thr Ser Pro Pro Ser Ser Pro Leu Ser Leu Pro Ala Val Thr Ser
7685 7690 7695

Pro His Pro Val Ser Thr Thr Phe Leu Ala His Ile Pro Pro Ser
7700 7705 7710

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Pro Leu  Pro Val Thr Ser Leu  Leu Thr Ser Gly Pro  Ala Thr Thr
    7715                 7720                 7725

Thr Asp  Ile Leu Gly Thr Ser  Thr Glu Pro Gly Thr  Ser Ser Ser
    7730                 7735                 7740

Ser Ser  Leu Ser Thr Thr Ser  His Glu Arg Leu Thr  Thr Tyr Lys
    7745                 7750                 7755

Asp Thr  Ala His Thr Glu Ala  Val His Pro Ser Thr  Asn Thr Gly
    7760                 7765                 7770

Gly Thr  Asn Val Ala Thr Thr  Ser Ser Gly Tyr Lys  Ser Gln Ser
    7775                 7780                 7785

Ser Val  Leu Ala Asp Ser Ser  Pro Met Cys Thr Thr  Ser Thr Met
    7790                 7795                 7800

Gly Asp  Thr Ser Val Leu Thr  Ser Thr Pro Ala Phe  Leu Glu Thr
    7805                 7810                 7815

Arg Arg  Ile Gln Thr Glu Leu  Ala Ser Ser Leu Thr  Pro Gly Leu
    7820                 7825                 7830

Arg Glu  Ser Ser Gly Ser Glu  Gly Thr Ser Ser Gly  Thr Lys Met
    7835                 7840                 7845

Ser Thr  Val Leu Ser Lys Val  Pro Thr Gly Ala Thr  Thr Glu Ile
    7850                 7855                 7860

Ser Lys  Glu Asp Val Thr Ser  Ile Pro Gly Pro Ala  Gln Ser Thr
    7865                 7870                 7875

Ile Ser  Pro Asp Ile Ser Thr  Arg Thr Val Ser Trp  Phe Ser Thr
    7880                 7885                 7890

Ser Pro  Val Met Thr Glu Ser  Ala Glu Ile Thr Met  Asn Thr His
    7895                 7900                 7905

Thr Ser  Pro Leu Gly Ala Thr  Thr Gln Gly Thr Ser  Thr Leu Asp
    7910                 7915                 7920

Thr Ser  Ser Thr Thr Ser Leu  Thr Met Thr His Ser  Thr Ile Ser
    7925                 7930                 7935

Gln Gly  Phe Ser His Ser Gln  Met Ser Thr Leu Met  Arg Arg Gly
    7940                 7945                 7950

Pro Glu  Asp Val Ser Trp Met  Ser Pro Pro Leu Leu  Glu Lys Thr
    7955                 7960                 7965

Arg Pro  Ser Phe Ser Leu Met  Ser Ser Pro Ala Thr  Thr Ser Pro
    7970                 7975                 7980

Ser Pro  Val Ser Ser Thr Leu  Pro Glu Ser Ile Ser  Ser Ser Pro
    7985                 7990                 7995

Leu Pro  Val Thr Ser Leu Leu  Thr Ser Gly Leu Ala  Lys Thr Thr
    8000                 8005                 8010

Asp Met  Leu His Lys Ser Ser  Glu Pro Val Thr Asn  Ser Pro Ala
    8015                 8020                 8025

Asn Leu  Ser Ser Thr Ser Val  Glu Ile Leu Ala Thr  Ser Glu Val
    8030                 8035                 8040

Thr Thr  Asp Thr Glu Lys Thr  His Pro Ser Ser Asn  Arg Thr Val
    8045                 8050                 8055

Thr Asp  Val Gly Thr Ser Ser  Ser Gly His Glu Ser  Thr Ser Phe
    8060                 8065                 8070

Val Leu  Ala Asp Ser Gln Thr  Ser Lys Val Thr Ser  Pro Met Val
    8075                 8080                 8085

Ile Thr  Ser Thr Met Glu Asp  Thr Ser Val Ser Thr  Ser Thr Pro
    8090                 8095                 8100

Gly Phe  Phe Glu Thr Ser Arg  Ile Gln Thr Glu Pro  Thr Ser Ser
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8105 8110 8115

Leu Thr Leu Gly Leu Arg Lys Thr Ser Ser Ser Glu Gly Thr Ser
8120 8125 8130

Leu Ala Thr Glu Met Ser Thr Val Leu Ser Gly Val Pro Thr Gly
8135 8140 8145

Ala Thr Ala Glu Val Ser Arg Thr Glu Val Thr Ser Ser Ser Arg
8150 8155 8160

Thr Ser Ile Ser Gly Phe Ala Gln Leu Thr Val Ser Pro Glu Thr
8165 8170 8175

Ser Thr Glu Thr Ile Thr Arg Leu Pro Thr Ser Ser Ile Met Thr
8180 8185 8190

Glu Ser Ala Glu Met Met Ile Lys Thr Gln Thr Asp Pro Pro Gly
8195 8200 8205

Ser Thr Pro Glu Ser Thr His Thr Val Asp Ile Ser Thr Thr Pro
8210 8215 8220

Asn Trp Val Glu Thr His Ser Thr Val Thr Gln Arg Phe Ser His
8225 8230 8235

Ser Glu Met Thr Thr Leu Val Ser Arg Ser Pro Gly Asp Met Leu
8240 8245 8250

Trp Pro Ser Gln Ser Ser Val Glu Glu Thr Ser Ser Ala Ser Ser
8255 8260 8265

Leu Leu Ser Leu Pro Ala Thr Thr Ser Pro Ser Pro Val Ser Ser
8270 8275 8280

Thr Leu Val Glu Asp Phe Pro Ser Ala Ser Leu Pro Val Thr Ser
8285 8290 8295

Leu Leu Asn Pro Gly Leu Val Ile Thr Thr Asp Arg Met Gly Ile
8300 8305 8310

Ser Arg Glu Pro Gly Thr Ser Ser Thr Ser Asn Leu Ser Ser Thr
8315 8320 8325

Ser His Glu Arg Leu Thr Thr Leu Glu Asp Thr Val Asp Thr Glu
8330 8335 8340

Asp Met Gln Pro Ser Thr His Thr Ala Val Thr Asn Val Arg Thr
8345 8350 8355

Ser Ile Ser Gly His Glu Ser Gln Ser Ser Val Leu Ser Asp Ser
8360 8365 8370

Glu Thr Pro Lys Ala Thr Ser Pro Met Gly Thr Thr Tyr Thr Met
8375 8380 8385

Gly Glu Thr Ser Val Ser Ile Ser Thr Ser Asp Phe Phe Glu Thr
8390 8395 8400

Ser Arg Ile Gln Ile Glu Pro Thr Ser Ser Leu Thr Ser Gly Leu
8405 8410 8415

Arg Glu Thr Ser Ser Ser Glu Arg Ile Ser Ser Ala Thr Glu Gly
8420 8425 8430

Ser Thr Val Leu Ser Glu Val Pro Ser Gly Ala Thr Thr Glu Val
8435 8440 8445

Ser Arg Thr Glu Val Ile Ser Ser Arg Gly Thr Ser Met Ser Gly
8450 8455 8460

Pro Asp Gln Phe Thr Ile Ser Pro Asp Ile Ser Thr Glu Ala Ile
8465 8470 8475

Thr Arg Leu Ser Thr Ser Pro Ile Met Thr Glu Ser Ala Glu Ser
8480 8485 8490

Ala Ile Thr Ile Glu Thr Gly Ser Pro Gly Ala Thr Ser Glu Gly
8495 8500 8505

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Thr Leu  Thr Leu Asp Thr Ser  Thr Thr Thr Phe Trp  Ser Gly Thr
    8510                 8515                 8520

His Ser  Thr Ala Ser Pro Gly  Phe Ser His Ser Glu  Met Thr Thr
    8525                 8530                 8535

Leu Met  Ser Arg Thr Pro Gly  Asp Val Pro Trp Pro  Ser Leu Pro
    8540                 8545                 8550

Ser Val  Glu Glu Ala Ser Ser  Val Ser Ser Ser Leu  Ser Ser Pro
    8555                 8560                 8565

Ala Met  Thr Ser Thr Ser Phe  Phe Ser Thr Leu Pro  Glu Ser Ile
    8570                 8575                 8580

Ser Ser  Ser Pro His Pro Val  Thr Ala Leu Leu Thr  Leu Gly Pro
    8585                 8590                 8595

Val Lys  Thr Thr Asp Met Leu  Arg Thr Ser Ser Glu  Pro Glu Thr
    8600                 8605                 8610

Ser Ser  Pro Pro Asn Leu Ser  Ser Thr Ser Ala Glu  Ile Leu Ala
    8615                 8620                 8625

Thr Ser  Glu Val Thr Lys Asp  Arg Glu Lys Ile His  Pro Ser Ser
    8630                 8635                 8640

Asn Thr  Pro Val Val Asn Val  Gly Thr Val Ile Tyr  Lys His Leu
    8645                 8650                 8655

Ser Pro  Ser Ser Val Leu Ala  Asp Leu Val Thr Thr  Lys Pro Thr
    8660                 8665                 8670

Ser Pro  Met Ala Thr Thr Ser  Thr Leu Gly Asn Thr  Ser Val Ser
    8675                 8680                 8685

Thr Ser  Thr Pro Ala Phe Pro  Glu Thr Met Met Thr  Gln Pro Thr
    8690                 8695                 8700

Ser Ser  Leu Thr Ser Gly Leu  Arg Glu Ile Ser Thr  Ser Gln Glu
    8705                 8710                 8715

Thr Ser  Ser Ala Thr Glu Arg  Ser Ala Ser Leu Ser  Gly Met Pro
    8720                 8725                 8730

Thr Gly  Ala Thr Thr Lys Val  Ser Arg Thr Glu Ala  Leu Ser Leu
    8735                 8740                 8745

Gly Arg  Thr Ser Thr Pro Gly  Pro Ala Gln Ser Thr  Ile Ser Pro
    8750                 8755                 8760

Glu Ile  Ser Thr Glu Thr Ile  Thr Arg Ile Ser Thr  Pro Leu Thr
    8765                 8770                 8775

Thr Thr  Gly Ser Ala Glu Met  Thr Ile Thr Pro Lys  Thr Gly His
    8780                 8785                 8790

Ser Gly  Ala Ser Ser Gln Gly  Thr Phe Thr Leu Asp  Thr Ser Ser
    8795                 8800                 8805

Arg Ala  Ser Trp Pro Gly Thr  His Ser Ala Ala Thr  His Arg Ser
    8810                 8815                 8820

Pro His  Ser Gly Met Thr Thr  Pro Met Ser Arg Gly  Pro Glu Asp
    8825                 8830                 8835

Val Ser  Trp Pro Ser Arg Pro  Ser Val Glu Lys Thr  Ser Pro Pro
    8840                 8845                 8850

Ser Ser  Leu Val Ser Leu Ser  Ala Val Thr Ser Pro  Ser Pro Leu
    8855                 8860                 8865

Tyr Ser  Thr Pro Ser Glu Ser  Ser His Ser Ser Pro  Leu Arg Val
    8870                 8875                 8880

Thr Ser  Leu Phe Thr Pro Val  Met Met Lys Thr Thr  Asp Met Leu
    8885                 8890                 8895
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Asp Thr  Ser Leu Glu Pro Val  Thr Thr Ser Pro Pro  Ser Met Asn
    8900                 8905                 8910

Ile Thr  Ser Asp Glu Ser Leu  Ala Thr Ser Lys Ala  Thr Met Glu
    8915                 8920                 8925

Thr Glu  Ala Ile Gln Leu Ser  Glu Asn Thr Ala Val  Thr Gln Met
    8930                 8935                 8940

Gly Thr  Ile Ser Ala Arg Gln  Glu Phe Tyr Ser Ser  Tyr Pro Gly
    8945                 8950                 8955

Leu Pro  Glu Pro Ser Lys Val  Thr Ser Pro Val Val  Thr Ser Ser
    8960                 8965                 8970

Thr Ile  Lys Asp Ile Val Ser  Thr Thr Ile Pro Ala  Ser Ser Glu
    8975                 8980                 8985

Ile Thr  Arg Ile Glu Met Glu  Ser Thr Ser Thr Leu  Thr Pro Thr
    8990                 8995                 9000

Pro Arg  Glu Thr Ser Thr Ser  Gln Glu Ile His Ser  Ala Thr Lys
    9005                 9010                 9015

Pro Ser  Thr Val Pro Tyr Lys  Ala Leu Thr Ser Ala  Thr Ile Glu
    9020                 9025                 9030

Asp Ser  Met Thr Gln Val Met  Ser Ser Ser Arg Gly  Pro Ser Pro
    9035                 9040                 9045

Asp Gln  Ser Thr Met Ser Gln  Asp Ile Ser Thr Glu  Val Ile Thr
    9050                 9055                 9060

Arg Leu  Ser Thr Ser Pro Ile  Lys Thr Glu Ser Thr  Glu Met Thr
    9065                 9070                 9075

Ile Thr  Thr Gln Thr Gly Ser  Pro Gly Ala Thr Ser  Arg Gly Thr
    9080                 9085                 9090

Leu Thr  Leu Asp Thr Ser Thr  Thr Phe Met Ser Gly  Thr His Ser
    9095                 9100                 9105

Thr Ala  Ser Gln Gly Phe Ser  His Ser Gln Met Thr  Ala Leu Met
    9110                 9115                 9120

Ser Arg  Thr Pro Gly Asp Val  Pro Trp Leu Ser His  Pro Ser Val
    9125                 9130                 9135

Glu Glu  Ala Ser Ser Ala Ser  Phe Ser Leu Ser Ser  Pro Val Met
    9140                 9145                 9150

Thr Ser  Ser Ser Pro Val Ser  Ser Thr Leu Pro Asp  Ser Ile His
    9155                 9160                 9165

Ser Ser  Ser Leu Pro Val Thr  Ser Leu Leu Thr Ser  Gly Leu Val
    9170                 9175                 9180

Lys Thr  Thr Glu Leu Leu Gly  Thr Ser Ser Glu Pro  Glu Thr Ser
    9185                 9190                 9195

Ser Pro  Pro Asn Leu Ser Ser  Thr Ser Ala Glu Ile  Leu Ala Ile
    9200                 9205                 9210

Thr Glu  Val Thr Thr Asp Thr  Glu Lys Leu Glu Met  Thr Asn Val
    9215                 9220                 9225

Val Thr  Ser Gly Tyr Thr His  Glu Ser Pro Ser Ser  Val Leu Ala
    9230                 9235                 9240

Asp Ser  Val Thr Thr Lys Ala  Thr Ser Ser Met Gly  Ile Thr Tyr
    9245                 9250                 9255

Pro Thr  Gly Asp Thr Asn Val  Leu Thr Ser Thr Pro  Ala Phe Ser
    9260                 9265                 9270

Asp Thr  Ser Arg Ile Gln Thr  Lys Ser Lys Leu Ser  Leu Thr Pro
    9275                 9280                 9285

Gly Leu  Met Glu Thr Ser Ile  Ser Glu Glu Thr Ser  Ser Ala Thr
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    9290                9295                9300

Glu Lys  Ser Thr Val Leu Ser  Ser Val Pro Thr Gly  Ala Thr Thr
    9305                9310                9315

Glu Val  Ser Arg Thr Glu Ala  Ile Ser Ser Ser Arg  Thr Ser Ile
    9320                9325                9330

Pro Gly  Pro Ala Gln Ser Thr  Met Ser Ser Asp Thr  Ser Met Glu
    9335                9340                9345

Thr Ile  Thr Arg Ile Ser Thr  Pro Leu Thr Arg Lys  Glu Ser Thr
    9350                9355                9360

Asp Met  Ala Ile Thr Pro Lys  Thr Gly Pro Ser Gly  Ala Thr Ser
    9365                9370                9375

Gln Gly  Thr Phe Thr Leu Asp  Ser Ser Ser Thr Ala  Ser Trp Pro
    9380                9385                9390

Gly Thr  His Ser Ala Thr Thr  Gln Arg Phe Pro Gln  Ser Val Val
    9395                9400                9405

Thr Thr  Pro Met Ser Arg Gly  Pro Glu Asp Val Ser  Trp Pro Ser
    9410                9415                9420

Pro Leu  Ser Val Glu Lys Asn  Ser Pro Pro Ser Ser  Leu Val Ser
    9425                9430                9435

Ser Ser  Ser Val Thr Ser Pro  Ser Pro Leu Tyr Ser  Thr Pro Ser
    9440                9445                9450

Gly Ser  Ser His Ser Ser Pro  Val Pro Val Thr Ser  Leu Phe Thr
    9455                9460                9465

Ser Ile  Met Met Lys Ala Thr  Asp Met Leu Asp Ala  Ser Leu Glu
    9470                9475                9480

Pro Glu  Thr Thr Ser Ala Pro  Asn Met Asn Ile Thr  Ser Asp Glu
    9485                9490                9495

Ser Leu  Ala Ala Ser Lys Ala  Thr Thr Glu Thr Glu  Ala Ile His
    9500                9505                9510

Val Phe  Glu Asn Thr Ala Ala  Ser His Val Glu Thr  Thr Ser Ala
    9515                9520                9525

Thr Glu  Glu Leu Tyr Ser Ser  Ser Pro Gly Phe Ser  Glu Pro Thr
    9530                9535                9540

Lys Val  Ile Ser Pro Val Val  Thr Ser Ser Ser Ile  Arg Asp Asn
    9545                9550                9555

Met Val  Ser Thr Thr Met Pro  Gly Ser Ser Gly Ile  Thr Arg Ile
    9560                9565                9570

Glu Ile  Glu Ser Met Ser Ser  Leu Thr Pro Gly Leu  Arg Glu Thr
    9575                9580                9585

Arg Thr  Ser Gln Asp Ile Thr  Ser Ser Thr Glu Thr  Ser Thr Val
    9590                9595                9600

Leu Tyr  Lys Met Pro Ser Gly  Ala Thr Pro Glu Val  Ser Arg Thr
    9605                9610                9615

Glu Val  Met Pro Ser Ser Arg  Thr Ser Ile Pro Gly  Pro Ala Gln
    9620                9625                9630

Ser Thr  Met Ser Leu Asp Ile  Ser Asp Glu Val Val  Thr Arg Leu
    9635                9640                9645

Ser Thr  Ser Pro Ile Met Thr  Glu Ser Ala Glu Ile  Thr Ile Thr
    9650                9655                9660

Thr Gln  Thr Gly Tyr Ser Leu  Ala Thr Ser Gln Val  Thr Leu Pro
    9665                9670                9675

Leu Gly  Thr Ser Met Thr Phe  Leu Ser Gly Thr His  Ser Thr Met
    9680                9685                9690
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Ser Gln  Gly Leu Ser His Ser  Glu Met Thr Asn Leu  Met Ser Arg
    9695                 9700                 9705

Gly Pro  Glu Ser Leu Ser Trp  Thr Ser Pro Arg Phe  Val Glu Thr
    9710                 9715                 9720

Thr Arg  Ser Ser Ser Ser Leu  Thr Ser Leu Pro Leu  Thr Thr Ser
    9725                 9730                 9735

Leu Ser  Pro Val Ser Ser Thr  Leu Leu Asp Ser Ser  Pro Ser Ser
    9740                 9745                 9750

Pro Leu  Pro Val Thr Ser Leu  Ile Leu Pro Gly Leu  Val Lys Thr
    9755                 9760                 9765

Thr Glu  Val Leu Asp Thr Ser  Ser Glu Pro Lys Thr  Ser Ser Ser
    9770                 9775                 9780

Pro Asn  Leu Ser Ser Thr Ser  Val Glu Ile Pro Ala  Thr Ser Glu
    9785                 9790                 9795

Ile Met  Thr Asp Thr Glu Lys  Ile His Pro Ser Ser  Asn Thr Ala
    9800                 9805                 9810

Val Ala  Lys Val Arg Thr Ser  Ser Ser Val His Glu  Ser His Ser
    9815                 9820                 9825

Ser Val  Leu Ala Asp Ser Glu  Thr Thr Ile Thr Ile  Pro Ser Met
    9830                 9835                 9840

Gly Ile  Thr Ser Ala Val Asp  Asp Thr Thr Val Phe  Thr Ser Asn
    9845                 9850                 9855

Pro Ala  Phe Ser Glu Thr Arg  Arg Ile Pro Thr Glu  Pro Thr Phe
    9860                 9865                 9870

Ser Leu  Thr Pro Gly Phe Arg  Glu Thr Ser Thr Ser  Glu Glu Thr
    9875                 9880                 9885

Thr Ser  Ile Thr Glu Thr Ser  Ala Val Leu Tyr Gly  Val Pro Thr
    9890                 9895                 9900

Ser Ala  Thr Thr Glu Val Ser  Met Thr Glu Ile Met  Ser Ser Asn
    9905                 9910                 9915

Arg Ile  His Ile Pro Asp Ser  Asp Gln Ser Thr Met  Ser Pro Asp
    9920                 9925                 9930

Ile Ile  Thr Glu Val Ile Thr  Arg Leu Ser Ser Ser  Ser Met Met
    9935                 9940                 9945

Ser Glu  Ser Thr Gln Met Thr  Ile Thr Thr Gln Lys  Ser Ser Pro
    9950                 9955                 9960

Gly Ala  Thr Ala Gln Ser Thr  Leu Thr Leu Ala Thr  Thr Thr Ala
    9965                 9970                 9975

Pro Leu  Ala Arg Thr His Ser  Thr Val Pro Pro Arg  Phe Leu His
    9980                 9985                 9990

Ser Glu  Met Thr Thr Leu Met   Ser Arg Ser Pro Glu   Asn Pro Ser
    9995                 10000                10005

Trp Lys   Ser Ser Leu Phe Val   Glu Lys Thr Ser Ser   Ser Ser Ser
    10010                10015                10020

Leu Leu   Ser Leu Pro Val Thr   Thr Ser Pro Ser Val   Ser Ser Thr
    10025                10030                10035

Leu Pro   Gln Ser Ile Pro Ser   Ser Ser Phe Ser Val   Thr Ser Leu
    10040                10045                10050

Leu Thr   Pro Gly Met Val Lys   Thr Thr Asp Thr Ser   Thr Glu Pro
    10055                10060                10065

Gly Thr   Ser Leu Ser Pro Asn   Leu Ser Gly Thr Ser   Val Glu Ile
    10070                10075                10080
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Leu Ala   Ala Ser Glu Val Thr   Thr Asp Thr Glu Lys   Ile His Pro
    10085                10090                10095

Ser Ser   Ser Met Ala Val Thr   Asn Val Gly Thr Thr   Ser Ser Gly
    10100                10105                10110

His Glu   Leu Tyr Ser Ser Val   Ser Ile His Ser Glu   Pro Ser Lys
    10115                10120                10125

Ala Thr   Tyr Pro Val Gly Thr   Pro Ser Ser Met Ala   Glu Thr Ser
    10130                10135                10140

Ile Ser   Thr Ser Met Pro Ala   Asn Phe Glu Thr Thr   Gly Phe Glu
    10145                10150                10155

Ala Glu   Pro Phe Ser His Leu   Thr Ser Gly Phe Arg   Lys Thr Asn
    10160                10165                10170

Met Ser   Leu Asp Thr Ser Ser   Val Thr Pro Thr Asn   Thr Pro Ser
    10175                10180                10185

Ser Pro   Gly Ser Thr His Leu   Leu Gln Ser Ser Lys   Thr Asp Phe
    10190                10195                10200

Thr Ser   Ser Ala Lys Thr Ser   Ser Pro Asp Trp Pro   Pro Ala Ser
    10205                10210                10215

Gln Tyr   Thr Glu Ile Pro Val   Asp Ile Ile Thr Pro   Phe Asn Ala
    10220                10225                10230

Ser Pro   Ser Ile Thr Glu Ser   Thr Gly Ile Thr Ser   Phe Pro Glu
    10235                10240                10245

Ser Arg   Phe Thr Met Ser Val   Thr Glu Ser Thr His   His Leu Ser
    10250                10255                10260

Thr Asp   Leu Leu Pro Ser Ala   Glu Thr Ile Ser Thr   Gly Thr Val
    10265                10270                10275

Met Pro   Ser Leu Ser Glu Ala   Met Thr Ser Phe Ala   Thr Thr Gly
    10280                10285                10290

Val Pro   Arg Ala Ile Ser Gly   Ser Gly Ser Pro Phe   Ser Arg Thr
    10295                10300                10305

Glu Ser   Gly Pro Gly Asp Ala   Thr Leu Ser Thr Ile   Ala Glu Ser
    10310                10315                10320

Leu Pro   Ser Ser Thr Pro Val   Pro Phe Ser Ser Ser   Thr Phe Thr
    10325                10330                10335

Thr Thr   Asp Ser Ser Thr Ile   Pro Ala Leu His Glu   Ile Thr Ser
    10340                10345                10350

Ser Ser   Ala Thr Pro Tyr Arg   Val Asp Thr Ser Leu   Gly Thr Glu
    10355                10360                10365

Ser Ser   Thr Thr Glu Gly Arg   Leu Val Met Val Ser   Thr Leu Asp
    10370                10375                10380

Thr Ser   Ser Gln Pro Gly Arg   Thr Ser Ser Ser Pro   Ile Leu Asp
    10385                10390                10395

Thr Arg   Met Thr Glu Ser Val   Glu Leu Gly Thr Val   Thr Ser Ala
    10400                10405                10410

Tyr Gln   Val Pro Ser Leu Ser   Thr Arg Leu Thr Arg   Thr Asp Gly
    10415                10420                10425

Ile Met   Glu His Ile Thr Lys   Ile Pro Asn Glu Ala   Ala His Arg
    10430                10435                10440

Gly Thr   Ile Arg Pro Val Lys   Gly Pro Gln Thr Ser   Thr Ser Pro
    10445                10450                10455

Ala Ser   Pro Lys Gly Leu His   Thr Gly Gly Thr Lys   Arg Met Glu
    10460                10465                10470

Thr Thr   Thr Thr Ala Leu Lys   Thr Thr Thr Thr Ala   Leu Lys Thr
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10475 10480 10485

Thr Ser Arg Ala Thr Leu Thr Thr Ser Val Tyr Thr Pro Thr Leu
10490 10495 10500

Gly Thr Leu Thr Pro Leu Asn Ala Ser Met Gln Met Ala Ser Thr
10505 10510 10515

Ile Pro Thr Glu Met Met Ile Thr Thr Pro Tyr Val Phe Pro Asp
10520 10525 10530

Val Pro Glu Thr Thr Ser Ser Leu Ala Thr Ser Leu Gly Ala Glu
10535 10540 10545

Thr Ser Thr Ala Leu Pro Arg Thr Thr Pro Ser Val Phe Asn Arg
10550 10555 10560

Glu Ser Glu Thr Thr Ala Ser Leu Val Ser Arg Ser Gly Ala Glu
10565 10570 10575

Arg Ser Pro Val Ile Gln Thr Leu Asp Val Ser Ser Ser Glu Pro
10580 10585 10590

Asp Thr Thr Ala Ser Trp Val Ile His Pro Ala Glu Thr Ile Pro
10595 10600 10605

Thr Val Ser Lys Thr Thr Pro Asn Phe Phe His Ser Glu Leu Asp
10610 10615 10620

Thr Val Ser Ser Thr Ala Thr Ser His Gly Ala Asp Val Ser Ser
10625 10630 10635

Ala Ile Pro Thr Asn Ile Ser Pro Ser Glu Leu Asp Ala Leu Thr
10640 10645 10650

Pro Leu Val Thr Ile Ser Gly Thr Asp Thr Ser Thr Thr Phe Pro
10655 10660 10665

Thr Leu Thr Lys Ser Pro His Glu Thr Glu Thr Arg Thr Thr Trp
10670 10675 10680

Leu Thr His Pro Ala Glu Thr Ser Ser Thr Ile Pro Arg Thr Ile
10685 10690 10695

Pro Asn Phe Ser His His Glu Ser Asp Ala Thr Pro Ser Ile Ala
10700 10705 10710

Thr Ser Pro Gly Ala Glu Thr Ser Ser Ala Ile Pro Ile Met Thr
10715 10720 10725

Val Ser Pro Gly Ala Glu Asp Leu Val Thr Ser Gln Val Thr Ser
10730 10735 10740

Ser Gly Thr Asp Arg Asn Met Thr Ile Pro Thr Leu Thr Leu Ser
10745 10750 10755

Pro Gly Glu Pro Lys Thr Ile Ala Ser Leu Val Thr His Pro Glu
10760 10765 10770

Ala Gln Thr Ser Ser Ala Ile Pro Thr Ser Thr Ile Ser Pro Ala
10775 10780 10785

Val Ser Arg Leu Val Thr Ser Met Val Thr Ser Leu Ala Ala Lys
10790 10795 10800

Thr Ser Thr Thr Asn Arg Ala Leu Thr Asn Ser Pro Gly Glu Pro
10805 10810 10815

Ala Thr Thr Val Ser Leu Val Thr His Pro Ala Gln Thr Ser Pro
10820 10825 10830

Thr Val Pro Trp Thr Thr Ser Ile Phe Phe His Ser Lys Ser Asp
10835 10840 10845

Thr Thr Pro Ser Met Thr Thr Ser His Gly Ala Glu Ser Ser Ser
10850 10855 10860

Ala Val Pro Thr Pro Thr Val Ser Thr Glu Val Pro Gly Val Val
10865 10870 10875

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Thr Pro   Leu Val Thr Ser Ser   Arg Ala Val Ile Ser   Thr Thr Ile
    10880                   10885                   10890

Pro Ile   Leu Thr Leu Ser Pro   Gly Glu Pro Glu Thr   Thr Pro Ser
    10895                   10900                   10905

Met Ala   Thr Ser His Gly Glu   Glu Ala Ser Ser Ala   Ile Pro Thr
    10910                   10915                   10920

Pro Thr   Val Ser Pro Gly Val   Pro Gly Val Val Thr   Ser Leu Val
    10925                   10930                   10935

Thr Ser   Ser Arg Ala Val Thr   Ser Thr Thr Ile Pro   Ile Leu Thr
    10940                   10945                   10950

Phe Ser   Leu Gly Glu Pro Glu   Thr Thr Pro Ser Met   Ala Thr Ser
    10955                   10960                   10965

His Gly   Thr Glu Ala Gly Ser   Ala Val Pro Thr Val   Leu Pro Glu
    10970                   10975                   10980

Val Pro   Gly Met Val Thr Ser   Leu Val Ala Ser Ser   Arg Ala Val
    10985                   10990                   10995

Thr Ser   Thr Thr Leu Pro Thr   Leu Thr Leu Ser Pro   Gly Glu Pro
    11000                   11005                   11010

Glu Thr   Thr Pro Ser Met Ala   Thr Ser His Gly Ala   Glu Ala Ser
    11015                   11020                   11025

Ser Thr   Val Pro Thr Val Ser   Pro Glu Val Pro Gly   Val Val Thr
    11030                   11035                   11040

Ser Leu   Val Thr Ser Ser Ser   Gly Val Asn Ser Thr   Ser Ile Pro
    11045                   11050                   11055

Thr Leu   Ile Leu Ser Pro Gly   Glu Leu Glu Thr Thr   Pro Ser Met
    11060                   11065                   11070

Ala Thr   Ser His Gly Ala Glu   Ala Ser Ser Ala Val   Pro Thr Pro
    11075                   11080                   11085

Thr Val   Ser Pro Gly Val Ser   Gly Val Val Thr Pro   Leu Val Thr
    11090                   11095                   11100

Ser Ser   Arg Ala Val Thr Ser   Thr Thr Ile Pro Ile   Leu Thr Leu
    11105                   11110                   11115

Ser Ser   Ser Glu Pro Glu Thr   Thr Pro Ser Met Ala   Thr Ser His
    11120                   11125                   11130

Gly Val   Glu Ala Ser Ser Ala   Val Leu Thr Val Ser   Pro Glu Val
    11135                   11140                   11145

Pro Gly   Met Val Thr Ser Leu   Val Thr Ser Ser Arg   Ala Val Thr
    11150                   11155                   11160

Ser Thr   Thr Ile Pro Thr Leu   Thr Ile Ser Ser Asp   Glu Pro Glu
    11165                   11170                   11175

Thr Thr   Thr Ser Leu Val Thr   His Ser Glu Ala Lys   Met Ile Ser
    11180                   11185                   11190

Ala Ile   Pro Thr Leu Ala Val   Ser Pro Thr Val Gln   Gly Leu Val
    11195                   11200                   11205

Thr Ser   Leu Val Thr Ser Ser   Gly Ser Glu Thr Ser   Ala Phe Ser
    11210                   11215                   11220

Asn Leu   Thr Val Ala Ser Ser   Gln Pro Glu Thr Ile   Asp Ser Trp
    11225                   11230                   11235

Val Ala   His Pro Gly Thr Glu   Ala Ser Ser Val Val   Pro Thr Leu
    11240                   11245                   11250

Thr Val   Ser Thr Gly Glu Pro   Phe Thr Asn Ile Ser   Leu Val Thr
    11255                   11260                   11265
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His Pro   Ala Glu Ser Ser Ser   Thr Leu Pro Arg Thr   Thr Ser Arg
    11270                 11275                 11280

Phe Ser   His Ser Glu Leu Asp   Thr Met Pro Ser Thr   Val Thr Ser
    11285                 11290                 11295

Pro Glu   Ala Glu Ser Ser Ser   Ala Ile Ser Thr Thr   Ile Ser Pro
    11300                 11305                 11310

Gly Ile   Pro Gly Val Leu Thr   Ser Leu Val Thr Ser   Ser Gly Arg
    11315                 11320                 11325

Asp Ile   Ser Ala Thr Phe Pro   Thr Val Pro Glu Ser   Pro His Glu
    11330                 11335                 11340

Ser Glu   Ala Thr Ala Ser Trp   Val Thr His Pro Ala   Val Thr Ser
    11345                 11350                 11355

Thr Thr   Val Pro Arg Thr Thr   Pro Asn Tyr Ser His   Ser Glu Pro
    11360                 11365                 11370

Asp Thr   Thr Pro Ser Ile Ala   Thr Ser Pro Gly Ala   Glu Ala Thr
    11375                 11380                 11385

Ser Asp   Phe Pro Thr Ile Thr   Val Ser Pro Asp Val   Pro Asp Met
    11390                 11395                 11400

Val Thr   Ser Gln Val Thr Ser   Ser Gly Thr Asp Thr   Ser Ile Thr
    11405                 11410                 11415

Ile Pro   Thr Leu Thr Leu Ser   Ser Gly Glu Pro Glu   Thr Thr Thr
    11420                 11425                 11430

Ser Phe   Ile Thr Tyr Ser Glu   Thr His Thr Ser Ser   Ala Ile Pro
    11435                 11440                 11445

Thr Leu   Pro Val Ser Pro Gly   Ala Ser Lys Met Leu   Thr Ser Leu
    11450                 11455                 11460

Val Ile   Ser Ser Gly Thr Asp   Ser Thr Thr Thr Phe   Pro Thr Leu
    11465                 11470                 11475

Thr Glu   Thr Pro Tyr Glu Pro   Glu Thr Thr Ala Ile   Gln Leu Ile
    11480                 11485                 11490

His Pro   Ala Glu Thr Asn Thr   Met Val Pro Arg Thr   Thr Pro Lys
    11495                 11500                 11505

Phe Ser   His Ser Lys Ser Asp   Thr Thr Leu Pro Val   Ala Ile Thr
    11510                 11515                 11520

Ser Pro   Gly Pro Glu Ala Ser   Ser Ala Val Ser Thr   Thr Thr Ile
    11525                 11530                 11535

Ser Pro   Asp Met Ser Asp Leu   Val Thr Ser Leu Val   Pro Ser Ser
    11540                 11545                 11550

Gly Thr   Asp Thr Ser Thr Thr   Phe Pro Thr Leu Ser   Glu Thr Pro
    11555                 11560                 11565

Tyr Glu   Pro Glu Thr Thr Ala   Thr Trp Leu Thr His   Pro Ala Glu
    11570                 11575                 11580

Thr Ser   Thr Thr Val Ser Gly   Thr Ile Pro Asn Phe   Ser His Arg
    11585                 11590                 11595

Gly Ser   Asp Thr Ala Pro Ser   Met Val Thr Ser Pro   Gly Val Asp
    11600                 11605                 11610

Thr Arg   Ser Gly Val Pro Thr   Thr Thr Ile Pro Pro   Ser Ile Pro
    11615                 11620                 11625

Gly Val   Val Thr Ser Gln Val   Thr Ser Ser Ala Thr   Asp Thr Ser
    11630                 11635                 11640

Thr Ala   Ile Pro Thr Leu Thr   Pro Ser Pro Gly Glu   Pro Glu Thr
    11645                 11650                 11655

Thr Ala   Ser Ser Ala Thr His   Pro Gly Thr Gln Thr   Gly Phe Thr
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    11660                11665                11670

Val Pro   Ile Arg Thr Val Pro   Ser Ser Glu Pro Asp   Thr Met Ala
    11675                11680                11685

Ser Trp   Val Thr His Pro Pro   Gln Thr Ser Thr Pro   Val Ser Arg
    11690                11695                11700

Thr Thr   Ser Ser Phe Ser His   Ser Ser Pro Asp Ala   Thr Pro Val
    11705                11710                11715

Met Ala   Thr Ser Pro Arg Thr   Glu Ala Ser Ser Ala   Val Leu Thr
    11720                11725                11730

Thr Ile   Ser Pro Gly Ala Pro   Glu Met Val Thr Ser   Gln Ile Thr
    11735                11740                11745

Ser Ser   Gly Ala Ala Thr Ser   Thr Thr Val Pro Thr   Leu Thr His
    11750                11755                11760

Ser Pro   Gly Met Pro Glu Thr   Thr Ala Leu Leu Ser   Thr His Pro
    11765                11770                11775

Arg Thr   Glu Thr Ser Lys Thr   Phe Pro Ala Ser Thr   Val Phe Pro
    11780                11785                11790

Gln Val   Ser Glu Thr Thr Ala   Ser Leu Thr Ile Arg   Pro Gly Ala
    11795                11800                11805

Glu Thr   Ser Thr Ala Leu Pro   Thr Gln Thr Thr Ser   Ser Leu Phe
    11810                11815                11820

Thr Leu   Leu Val Thr Gly Thr   Ser Arg Val Asp Leu   Ser Pro Thr
    11825                11830                11835

Ala Ser   Pro Gly Val Ser Ala   Lys Thr Ala Pro Leu   Ser Thr His
    11840                11845                11850

Pro Gly   Thr Glu Thr Ser Thr   Met Ile Pro Thr Ser   Thr Leu Ser
    11855                11860                11865

Leu Gly   Leu Leu Glu Thr Thr   Gly Leu Leu Ala Thr   Ser Ser Ser
    11870                11875                11880

Ala Glu   Thr Ser Thr Ser Thr   Leu Thr Leu Thr Val   Ser Pro Ala
    11885                11890                11895

Val Ser   Gly Leu Ser Ser Ala   Ser Ile Thr Thr Asp   Lys Pro Gln
    11900                11905                11910

Thr Val   Thr Ser Trp Asn Thr   Glu Thr Ser Pro Ser   Val Thr Ser
    11915                11920                11925

Val Gly   Pro Pro Glu Phe Ser   Arg Thr Val Thr Gly   Thr Thr Met
    11930                11935                11940

Thr Leu   Ile Pro Ser Glu Met   Pro Thr Pro Pro Lys   Thr Ser His
    11945                11950                11955

Gly Glu   Gly Val Ser Pro Thr   Thr Ile Leu Arg Thr   Thr Met Val
    11960                11965                11970

Glu Ala   Thr Asn Leu Ala Thr   Thr Gly Ser Ser Pro   Thr Val Ala
    11975                11980                11985

Lys Thr   Thr Thr Thr Phe Asn   Thr Leu Ala Gly Ser   Leu Phe Thr
    11990                11995                12000

Pro Leu   Thr Thr Pro Gly Met   Ser Thr Leu Ala Ser   Glu Ser Val
    12005                12010                12015

Thr Ser   Arg Thr Ser Tyr Asn   His Arg Ser Trp Ile   Ser Thr Thr
    12020                12025                12030

Ser Ser   Tyr Asn Arg Arg Tyr   Trp Thr Pro Ala Thr   Ser Thr Pro
    12035                12040                12045

Val Thr   Ser Thr Phe Ser Pro   Gly Ile Ser Thr Ser   Ser Ile Pro
    12050                12055                12060
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Ser Ser   Thr Ala Ala Thr Val   Pro Phe Met Val Pro   Phe Thr Leu
    12065                 12070                 12075

Asn Phe   Thr Ile Thr Asn Leu   Gln Tyr Glu Glu Asp   Met Arg His
    12080                 12085                 12090

Pro Gly   Ser Arg Lys Phe Asn   Ala Thr Glu Arg Glu   Leu Gln Gly
    12095                 12100                 12105

Leu Leu   Lys Pro Leu Phe Arg   Asn Ser Ser Leu Glu   Tyr Leu Tyr
    12110                 12115                 12120

Ser Gly   Cys Arg Leu Ala Ser   Leu Arg Pro Glu Lys   Asp Ser Ser
    12125                 12130                 12135

Ala Thr   Ala Val Asp Ala Ile   Cys Thr His Arg Pro   Asp Pro Glu
    12140                 12145                 12150

Asp Leu   Gly Leu Asp Arg Glu   Arg Leu Tyr Trp Glu   Leu Ser Asn
    12155                 12160                 12165

Leu Thr   Asn Gly Ile Gln Glu   Leu Gly Pro Tyr Thr   Leu Asp Arg
    12170                 12175                 12180

Asn Ser   Leu Tyr Val Asn Gly   Phe Thr His Arg Ser   Ser Met Pro
    12185                 12190                 12195

Thr Thr   Ser Thr Pro Gly Thr   Ser Thr Val Asp Val   Gly Thr Ser
    12200                 12205                 12210

Gly Thr   Pro Ser Ser Ser Pro   Ser Pro Thr Thr Ala   Gly Pro Leu
    12215                 12220                 12225

Leu Met   Pro Phe Thr Leu Asn   Phe Thr Ile Thr Asn   Leu Gln Tyr
    12230                 12235                 12240

Glu Glu   Asp Met Arg Arg Thr   Gly Ser Arg Lys Phe   Asn Thr Met
    12245                 12250                 12255

Glu Ser   Val Leu Gln Gly Leu   Leu Lys Pro Leu Phe   Lys Asn Thr
    12260                 12265                 12270

Ser Val   Gly Pro Leu Tyr Ser   Gly Cys Arg Leu Thr   Leu Leu Arg
    12275                 12280                 12285

Pro Glu   Lys Asp Gly Ala Ala   Thr Gly Val Asp Ala   Ile Cys Thr
    12290                 12295                 12300

His Arg   Leu Asp Pro Lys Ser   Pro Gly Leu Asn Arg   Glu Gln Leu
    12305                 12310                 12315

Tyr Trp   Glu Leu Ser Lys Leu   Thr Asn Asp Ile Glu   Glu Leu Gly
    12320                 12325                 12330

Pro Tyr   Thr Leu Asp Arg Asn   Ser Leu Tyr Val Asn   Gly Phe Thr
    12335                 12340                 12345

His Gln   Ser Ser Val Ser Thr   Thr Ser Thr Pro Gly   Thr Ser Thr
    12350                 12355                 12360

Val Asp   Leu Arg Thr Ser Gly   Thr Pro Ser Ser Leu   Ser Ser Pro
    12365                 12370                 12375

Thr Ile   Met Ala Ala Gly Pro   Leu Leu Val Pro Phe   Thr Leu Asn
    12380                 12385                 12390

Phe Thr   Ile Thr Asn Leu Gln   Tyr Gly Glu Asp Met   Gly His Pro
    12395                 12400                 12405

Gly Ser   Arg Lys Phe Asn Thr   Thr Glu Arg Val Leu   Gln Gly Leu
    12410                 12415                 12420

Leu Gly   Pro Ile Phe Lys Asn   Thr Ser Val Gly Pro   Leu Tyr Ser
    12425                 12430                 12435

Gly Cys   Arg Leu Thr Ser Leu   Arg Ser Glu Lys Asp   Gly Ala Ala
    12440                 12445                 12450
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Thr Gly   Val Asp Ala Ile Cys   Ile His His Leu Asp   Pro Lys Ser
    12455                 12460                 12465

Pro Gly   Leu Asn Arg Glu Arg   Leu Tyr Trp Glu Leu   Ser Gln Leu
    12470                 12475                 12480

Thr Asn   Gly Ile Lys Glu Leu   Gly Pro Tyr Thr Leu   Asp Arg Asn
    12485                 12490                 12495

Ser Leu   Tyr Val Asn Gly Phe   Thr His Arg Thr Ser   Val Pro Thr
    12500                 12505                 12510

Ser Ser   Thr Pro Gly Thr Ser   Thr Val Asp Leu Gly   Thr Ser Gly
    12515                 12520                 12525

Thr Pro   Phe Ser Leu Pro Ser   Pro Ala Thr Ala Gly   Pro Leu Leu
    12530                 12535                 12540

Val Leu   Phe Thr Leu Asn Phe   Thr Ile Thr Asn Leu   Lys Tyr Glu
    12545                 12550                 12555

Glu Asp   Met His Arg Pro Gly   Ser Arg Lys Phe Asn   Thr Thr Glu
    12560                 12565                 12570

Arg Val   Leu Gln Thr Leu Leu   Gly Pro Met Phe Lys   Asn Thr Ser
    12575                 12580                 12585

Val Gly   Leu Leu Tyr Ser Gly   Cys Arg Leu Thr Leu   Leu Arg Ser
    12590                 12595                 12600

Glu Lys   Asp Gly Ala Ala Thr   Gly Val Asp Ala Ile   Cys Thr His
    12605                 12610                 12615

Arg Leu   Asp Pro Lys Ser Pro   Gly Val Asp Arg Glu   Gln Leu Tyr
    12620                 12625                 12630

Trp Glu   Leu Ser Gln Leu Thr   Asn Gly Ile Lys Glu   Leu Gly Pro
    12635                 12640                 12645

Tyr Thr   Leu Asp Arg Asn Ser   Leu Tyr Val Asn Gly   Phe Thr His
    12650                 12655                 12660

Trp Ile   Pro Val Pro Thr Ser   Ser Thr Pro Gly Thr   Ser Thr Val
    12665                 12670                 12675

Asp Leu   Gly Ser Gly Thr Pro   Ser Ser Leu Pro Ser   Pro Thr Thr
    12680                 12685                 12690

Ala Gly   Pro Leu Leu Val Pro   Phe Thr Leu Asn Phe   Thr Ile Thr
    12695                 12700                 12705

Asn Leu   Lys Tyr Glu Glu Asp   Met His Cys Pro Gly   Ser Arg Lys
    12710                 12715                 12720

Phe Asn   Thr Thr Glu Arg Val   Leu Gln Ser Leu Leu   Gly Pro Met
    12725                 12730                 12735

Phe Lys   Asn Thr Ser Val Gly   Pro Leu Tyr Ser Gly   Cys Arg Leu
    12740                 12745                 12750

Thr Leu   Leu Arg Ser Glu Lys   Asp Gly Ala Ala Thr   Gly Val Asp
    12755                 12760                 12765

Ala Ile   Cys Thr His Arg Leu   Asp Pro Lys Ser Pro   Gly Val Asp
    12770                 12775                 12780

Arg Glu   Gln Leu Tyr Trp Glu   Leu Ser Gln Leu Thr   Asn Gly Ile
    12785                 12790                 12795

Lys Glu   Leu Gly Pro Tyr Thr   Leu Asp Arg Asn Ser   Leu Tyr Val
    12800                 12805                 12810

Asn Gly   Phe Thr His Gln Thr   Ser Ala Pro Asn Thr   Ser Thr Pro
    12815                 12820                 12825

Gly Thr   Ser Thr Val Asp Leu   Gly Thr Ser Gly Thr   Pro Ser Ser
    12830                 12835                 12840

Leu Pro   Ser Pro Thr Ser Ala   Gly Pro Leu Leu Val   Pro Phe Thr
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    12845                12850                12855

Leu Asn   Phe Thr Ile Thr Asn   Leu Gln Tyr Glu Glu   Asp Met His
    12860                12865                12870

His Pro   Gly Ser Arg Lys Phe   Asn Thr Thr Glu Arg   Val Leu Gln
    12875                12880                12885

Gly Leu   Leu Gly Pro Met Phe   Lys Asn Thr Ser Val   Gly Leu Leu
    12890                12895                12900

Tyr Ser   Gly Cys Arg Leu Thr   Leu Leu Arg Pro Glu   Lys Asn Gly
    12905                12910                12915

Ala Ala   Thr Gly Met Asp Ala   Ile Cys Ser His Arg   Leu Asp Pro
    12920                12925                12930

Lys Ser   Pro Gly Leu Asn Arg   Glu Gln Leu Tyr Trp   Glu Leu Ser
    12935                12940                12945

Gln Leu   Thr His Gly Ile Lys   Glu Leu Gly Pro Tyr   Thr Leu Asp
    12950                12955                12960

Arg Asn   Ser Leu Tyr Val Asn   Gly Phe Thr His Arg   Ser Ser Val
    12965                12970                12975

Ala Pro   Thr Ser Thr Pro Gly   Thr Ser Thr Val Asp   Leu Gly Thr
    12980                12985                12990

Ser Gly   Thr Pro Ser Ser Leu   Pro Ser Pro Thr Thr   Ala Val Pro
    12995                13000                13005

Leu Leu   Val Pro Phe Thr Leu   Asn Phe Thr Ile Thr   Asn Leu Gln
    13010                13015                13020

Tyr Gly   Glu Asp Met Arg His   Pro Gly Ser Arg Lys   Phe Asn Thr
    13025                13030                13035

Thr Glu   Arg Val Leu Gln Gly   Leu Leu Gly Pro Leu   Phe Lys Asn
    13040                13045                13050

Ser Ser   Val Gly Pro Leu Tyr   Ser Gly Cys Arg Leu   Ile Ser Leu
    13055                13060                13065

Arg Ser   Glu Lys Asp Gly Ala   Ala Thr Gly Val Asp   Ala Ile Cys
    13070                13075                13080

Thr His   His Leu Asn Pro Gln   Ser Pro Gly Leu Asp   Arg Glu Gln
    13085                13090                13095

Leu Tyr   Trp Gln Leu Ser Gln   Met Thr Asn Gly Ile   Lys Glu Leu
    13100                13105                13110

Gly Pro   Tyr Thr Leu Asp Arg   Asn Ser Leu Tyr Val   Asn Gly Phe
    13115                13120                13125

Thr His   Arg Ser Ser Gly Leu   Thr Thr Ser Thr Pro   Trp Thr Ser
    13130                13135                13140

Thr Val   Asp Leu Gly Thr Ser   Gly Thr Pro Ser Pro   Val Pro Ser
    13145                13150                13155

Pro Thr   Thr Thr Gly Pro Leu   Leu Val Pro Phe Thr   Leu Asn Phe
    13160                13165                13170

Thr Ile   Thr Asn Leu Gln Tyr   Glu Glu Asn Met Gly   His Pro Gly
    13175                13180                13185

Ser Arg   Lys Phe Asn Ile Thr   Glu Ser Val Leu Gln   Gly Leu Leu
    13190                13195                13200

Lys Pro   Leu Phe Lys Ser Thr   Ser Val Gly Pro Leu   Tyr Ser Gly
    13205                13210                13215

Cys Arg   Leu Thr Leu Leu Arg   Pro Glu Lys Asp Gly   Val Ala Thr
    13220                13225                13230

Arg Val   Asp Ala Ile Cys Thr   His Arg Pro Asp Pro   Lys Ile Pro
    13235                13240                13245
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Gly Leu   Asp Arg Gln Gln Leu   Tyr Trp Glu Leu Ser   Gln Leu Thr
    13250                 13255                 13260

His Ser   Ile Thr Glu Leu Gly   Pro Tyr Thr Leu Asp   Arg Asp Ser
    13265                 13270                 13275

Leu Tyr   Val Asn Gly Phe Thr   Gln Arg Ser Ser Val   Pro Thr Thr
    13280                 13285                 13290

Ser Thr   Pro Gly Thr Phe Thr   Val Gln Pro Glu Thr   Ser Glu Thr
    13295                 13300                 13305

Pro Ser   Ser Leu Pro Gly Pro   Thr Ala Thr Gly Pro   Val Leu Leu
    13310                 13315                 13320

Pro Phe   Thr Leu Asn Phe Thr   Ile Thr Asn Leu Gln   Tyr Glu Glu
    13325                 13330                 13335

Asp Met   Arg Arg Pro Gly Ser   Arg Lys Phe Asn Thr   Thr Glu Arg
    13340                 13345                 13350

Val Leu   Gln Gly Leu Leu Met   Pro Leu Phe Lys Asn   Thr Ser Val
    13355                 13360                 13365

Ser Ser   Leu Tyr Ser Gly Cys   Arg Leu Thr Leu Leu   Arg Pro Glu
    13370                 13375                 13380

Lys Asp   Gly Ala Ala Thr Arg   Val Asp Ala Val Cys   Thr His Arg
    13385                 13390                 13395

Pro Asp   Pro Lys Ser Pro Gly   Leu Asp Arg Glu Arg   Leu Tyr Trp
    13400                 13405                 13410

Lys Leu   Ser Gln Leu Thr His   Gly Ile Thr Glu Leu   Gly Pro Tyr
    13415                 13420                 13425

Thr Leu   Asp Arg His Ser Leu   Tyr Val Asn Gly Phe   Thr His Gln
    13430                 13435                 13440

Ser Ser   Met Thr Thr Thr Arg   Thr Pro Asp Thr Ser   Thr Met His
    13445                 13450                 13455

Leu Ala   Thr Ser Arg Thr Pro   Ala Ser Leu Ser Gly   Pro Met Thr
    13460                 13465                 13470

Ala Ser   Pro Leu Leu Val Leu   Phe Thr Ile Asn Phe   Thr Ile Thr
    13475                 13480                 13485

Asn Leu   Arg Tyr Glu Glu Asn   Met His His Pro Gly   Ser Arg Lys
    13490                 13495                 13500

Phe Asn   Thr Thr Glu Arg Val   Leu Gln Gly Leu Leu   Arg Pro Val
    13505                 13510                 13515

Phe Lys   Asn Thr Ser Val Gly   Pro Leu Tyr Ser Gly   Cys Arg Leu
    13520                 13525                 13530

Thr Leu   Leu Arg Pro Lys Lys   Asp Gly Ala Ala Thr   Lys Val Asp
    13535                 13540                 13545

Ala Ile   Cys Thr Tyr Arg Pro   Asp Pro Lys Ser Pro   Gly Leu Asp
    13550                 13555                 13560

Arg Glu   Gln Leu Tyr Trp Glu   Leu Ser Gln Leu Thr   His Ser Ile
    13565                 13570                 13575

Thr Glu   Leu Gly Pro Tyr Thr   Leu Asp Arg Asp Ser   Leu Tyr Val
    13580                 13585                 13590

Asn Gly   Phe Thr Gln Arg Ser   Ser Val Pro Thr Thr   Ser Ile Pro
    13595                 13600                 13605

Gly Thr   Pro Thr Val Asp Leu   Gly Thr Ser Gly Thr   Pro Val Ser
    13610                 13615                 13620

Lys Pro   Gly Pro Ser Ala Ala   Ser Pro Leu Leu Val   Leu Phe Thr
    13625                 13630                 13635
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Leu Asn   Phe Thr Ile Thr Asn   Leu Arg Tyr Glu Glu   Asn Met Gln
    13640                 13645                 13650

His Pro   Gly Ser Arg Lys Phe   Asn Thr Thr Glu Arg   Val Leu Gln
    13655                 13660                 13665

Gly Leu   Leu Arg Ser Leu Phe   Lys Ser Thr Ser Val   Gly Pro Leu
    13670                 13675                 13680

Tyr Ser   Gly Cys Arg Leu Thr   Leu Leu Arg Pro Glu   Lys Asp Gly
    13685                 13690                 13695

Thr Ala   Thr Gly Val Asp Ala   Ile Cys Thr His His   Pro Asp Pro
    13700                 13705                 13710

Lys Ser   Pro Arg Leu Asp Arg   Glu Gln Leu Tyr Trp   Glu Leu Ser
    13715                 13720                 13725

Gln Leu   Thr His Asn Ile Thr   Glu Leu Gly Pro Tyr   Ala Leu Asp
    13730                 13735                 13740

Asn Asp   Ser Leu Phe Val Asn   Gly Phe Thr His Arg   Ser Ser Val
    13745                 13750                 13755

Ser Thr   Thr Ser Thr Pro Gly   Thr Pro Thr Val Tyr   Leu Gly Ala
    13760                 13765                 13770

Ser Lys   Thr Pro Ala Ser Ile   Phe Gly Pro Ser Ala   Ala Ser His
    13775                 13780                 13785

Leu Leu   Ile Leu Phe Thr Leu   Asn Phe Thr Ile Thr   Asn Leu Arg
    13790                 13795                 13800

Tyr Glu   Glu Asn Met Trp Pro   Gly Ser Arg Lys Phe   Asn Thr Thr
    13805                 13810                 13815

Glu Arg   Val Leu Gln Gly Leu   Leu Arg Pro Leu Phe   Lys Asn Thr
    13820                 13825                 13830

Ser Val   Gly Pro Leu Tyr Ser   Gly Cys Arg Leu Thr   Leu Leu Arg
    13835                 13840                 13845

Pro Glu   Lys Asp Gly Glu Ala   Thr Gly Val Asp Ala   Ile Cys Thr
    13850                 13855                 13860

His Arg   Pro Asp Pro Thr Gly   Pro Gly Leu Asp Arg   Glu Gln Leu
    13865                 13870                 13875

Tyr Leu   Glu Leu Ser Gln Leu   Thr His Ser Ile Thr   Glu Leu Gly
    13880                 13885                 13890

Pro Tyr   Thr Leu Asp Arg Asp   Ser Leu Tyr Val Asn   Gly Phe Thr
    13895                 13900                 13905

His Arg   Ser Ser Val Pro Thr   Thr Ser Thr Gly Val   Val Ser Glu
    13910                 13915                 13920

Glu Pro   Phe Thr Leu Asn Phe   Thr Ile Asn Asn Leu   Arg Tyr Met
    13925                 13930                 13935

Ala Asp   Met Gly Gln Pro Gly   Ser Leu Lys Phe Asn   Ile Thr Asp
    13940                 13945                 13950

Asn Val   Met Gln His Leu Leu   Ser Pro Leu Phe Gln   Arg Ser Ser
    13955                 13960                 13965

Leu Gly   Ala Arg Tyr Thr Gly   Cys Arg Val Ile Ala   Leu Arg Ser
    13970                 13975                 13980

Val Lys   Asn Gly Ala Glu Thr   Arg Val Asp Leu Leu   Cys Thr Tyr
    13985                 13990                 13995

Leu Gln   Pro Leu Ser Gly Pro   Gly Leu Pro Ile Lys   Gln Val Phe
    14000                 14005                 14010

His Glu   Leu Ser Gln Gln Thr   His Gly Ile Thr Arg   Leu Gly Pro
    14015                 14020                 14025

Tyr Ser   Leu Asp Lys Asp Ser   Leu Tyr Leu Asn Gly   Tyr Asn Glu
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    14030                14035                14040

Pro Gly   Pro Asp Glu Pro Pro   Thr Thr Pro Lys Pro   Ala Thr Thr
    14045                14050                14055

Phe Leu   Pro Pro Leu Ser Glu   Ala Thr Thr Ala Met   Gly Tyr His
    14060                14065                14070

Leu Lys   Thr Leu Thr Leu Asn   Phe Thr Ile Ser Asn   Leu Gln Tyr
    14075                14080                14085

Ser Pro   Asp Met Gly Lys Gly   Ser Ala Thr Phe Asn   Ser Thr Glu
    14090                14095                14100

Gly Val   Leu Gln His Leu Leu   Arg Pro Leu Phe Gln   Lys Ser Ser
    14105                14110                14115

Met Gly   Pro Phe Tyr Leu Gly   Cys Gln Leu Ile Ser   Leu Arg Pro
    14120                14125                14130

Glu Lys   Asp Gly Ala Ala Thr   Gly Val Asp Thr Thr   Cys Thr Tyr
    14135                14140                14145

His Pro   Asp Pro Val Gly Pro   Gly Leu Asp Ile Gln   Gln Leu Tyr
    14150                14155                14160

Trp Glu   Leu Ser Gln Leu Thr   His Gly Val Thr Gln   Leu Gly Phe
    14165                14170                14175

Tyr Val   Leu Asp Arg Asp Ser   Leu Phe Ile Asn Gly   Tyr Ala Pro
    14180                14185                14190

Gln Asn   Leu Ser Ile Arg Gly   Glu Tyr Gln Ile Asn   Phe His Ile
    14195                14200                14205

Val Asn   Trp Asn Leu Ser Asn   Pro Asp Pro Thr Ser   Ser Glu Tyr
    14210                14215                14220

Ile Thr   Leu Leu Arg Asp Ile   Gln Asp Lys Val Thr   Thr Leu Tyr
    14225                14230                14235

Lys Gly   Ser Gln Leu His Asp   Thr Phe Arg Phe Cys   Leu Val Thr
    14240                14245                14250

Asn Leu   Thr Met Asp Ser Val   Leu Val Thr Val Lys   Ala Leu Phe
    14255                14260                14265

Ser Ser   Asn Leu Asp Pro Ser   Leu Val Glu Gln Val   Phe Leu Asp
    14270                14275                14280

Lys Thr   Leu Asn Ala Ser Phe   His Trp Leu Gly Ser   Thr Tyr Gln
    14285                14290                14295

Leu Val   Asp Ile His Val Thr   Glu Met Glu Ser Ser   Val Tyr Gln
    14300                14305                14310

Pro Thr   Ser Ser Ser Ser Thr   Gln His Phe Tyr Leu   Asn Phe Thr
    14315                14320                14325

Ile Thr   Asn Leu Pro Tyr Ser   Gln Asp Lys Ala Gln   Pro Gly Thr
    14330                14335                14340

Thr Asn   Tyr Gln Arg Asn Lys   Arg Asn Ile Glu Asp   Ala Leu Asn
    14345                14350                14355

Gln Leu   Phe Arg Asn Ser Ser   Ile Lys Ser Tyr Phe   Ser Asp Cys
    14360                14365                14370

Gln Val   Ser Thr Phe Arg Ser   Val Pro Asn Arg His   His Thr Gly
    14375                14380                14385

Val Asp   Ser Leu Cys Asn Phe   Ser Pro Leu Ala Arg   Arg Val Asp
    14390                14395                14400

Arg Val   Ala Ile Tyr Glu Glu   Phe Leu Arg Met Thr   Arg Asn Gly
    14405                14410                14415

Thr Gln   Leu Gln Asn Phe Thr   Leu Asp Arg Ser Ser   Val Leu Val
    14420                14425                14430
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Asp Gly   Tyr Ser Pro Asn Arg   Asn Glu Pro Leu Thr   Gly Asn Ser
    14435                 14440                 14445

Asp Leu   Pro Phe Trp Ala Val   Ile Leu Ile Gly Leu   Ala Gly Leu
    14450                 14455                 14460

Leu Gly   Val Ile Thr Cys Leu   Ile Cys Gly Val Leu   Val Thr Thr
    14465                 14470                 14475

Arg Arg   Arg Lys Lys Glu Gly   Glu Tyr Asn Val Gln   Gln Gln Cys
    14480                 14485                 14490

Pro Gly   Tyr Tyr Gln Ser His   Leu Asp Leu Glu Asp   Leu Gln
    14495                 14500                 14505
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<210> SEQ ID NO 58
<211> LENGTH: 630
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

```
Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
1               5                  10                  15

Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
            20                  25                  30

Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
        35                  40                  45

Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
    50                  55                  60

Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65                  70                  75                  80

Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
                85                  90                  95

Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
            100                 105                 110

Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
        115                 120                 125

Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
    130                 135                 140

Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145                 150                 155                 160

Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
                165                 170                 175

Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
            180                 185                 190

Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
        195                 200                 205

Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
    210                 215                 220

Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240

Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
                245                 250                 255

Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
            260                 265                 270

Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
        275                 280                 285

Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
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    290                 295                 300

Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305                 310                 315                 320

Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
                325                 330                 335

Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
            340                 345                 350

Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
        355                 360                 365

Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
    370                 375                 380

Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385                 390                 395                 400

Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu
                405                 410                 415

Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
            420                 425                 430

Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
        435                 440                 445

Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
    450                 455                 460

Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
465                 470                 475                 480

Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
                485                 490                 495

Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
            500                 505                 510

Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
        515                 520                 525

Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
    530                 535                 540

Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala
545                 550                 555                 560

Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
                565                 570                 575

Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
            580                 585                 590

Gly Tyr Leu Val Leu Asp Leu Ser Met Gln Glu Ala Leu Ser Gly Thr
        595                 600                 605

Pro Cys Leu Leu Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu
    610                 615                 620

Leu Ala Ser Thr Leu Ala
625                 630


<210> SEQ ID NO 59
<211> LENGTH: 622
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
1               5                   10                  15

Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
            20                  25                  30
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Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
        35                  40                  45

Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
    50                  55                  60

Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65                  70                  75                  80

Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
                85                  90                  95

Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
            100                 105                 110

Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
        115                 120                 125

Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
    130                 135                 140

Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145                 150                 155                 160

Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
                165                 170                 175

Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
            180                 185                 190

Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
        195                 200                 205

Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
    210                 215                 220

Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240

Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
                245                 250                 255

Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
            260                 265                 270

Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
        275                 280                 285

Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
    290                 295                 300

Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305                 310                 315                 320

Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
                325                 330                 335

Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
            340                 345                 350

Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
        355                 360                 365

Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
    370                 375                 380

Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385                 390                 395                 400

Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp
                405                 410                 415

Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr
            420                 425                 430

Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu
        435                 440                 445

Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp
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    450                 455                 460

Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
465                 470                 475                 480

Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
                485                 490                 495

Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
            500                 505                 510

Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
        515                 520                 525

Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
    530                 535                 540

Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
545                 550                 555                 560

Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
                565                 570                 575

Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
            580                 585                 590

Met Gln Glu Ala Leu Ser Gly Thr Pro Cys Leu Leu Gly Pro Gly Pro
        595                 600                 605

Val Leu Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala
    610                 615                 620


<210> SEQ ID NO 60
<211> LENGTH: 300
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
1               5                   10                  15

Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
            20                  25                  30

Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
        35                  40                  45

Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Thr Leu Pro Ser Lys Ser
    50                  55                  60

Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp
65                  70                  75                  80

Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp
                85                  90                  95

Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser
            100                 105                 110

Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala
        115                 120                 125

Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly
    130                 135                 140

Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe
145                 150                 155                 160

Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr
                165                 170                 175

Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro
            180                 185                 190

Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys
        195                 200                 205
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Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His
    210                 215                 220

Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser
225                 230                 235                 240

Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser
                245                 250                 255

Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val
            260                 265                 270

Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile
        275                 280                 285

Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
    290                 295                 300


<210> SEQ ID NO 61
<211> LENGTH: 314
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
1               5                   10                  15

Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
            20                  25                  30

Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
        35                  40                  45

Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Asn Ala Val Ser Ser Glu
    50                  55                  60

Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro Ser Lys Ser Asn Glu
65                  70                  75                  80

Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp Asp His
                85                  90                  95

Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp Val Asp
            100                 105                 110

Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser Asp Glu
        115                 120                 125

Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala Thr Glu
    130                 135                 140

Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly Arg Gly
145                 150                 155                 160

Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe Arg Arg
                165                 170                 175

Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr Ser His
            180                 185                 190

Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro Val Ala
        195                 200                 205

Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys Asp Ser
    210                 215                 220

Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His Ser His
225                 230                 235                 240

Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser Asn Glu
                245                 250                 255

His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser Arg Glu
            260                 265                 270

Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val Val Asp
        275                 280                 285
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Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile Ser His
290 295 300

Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
305 310

<210> SEQ ID NO 62
<211> LENGTH: 287
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
1 5 10 15

Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Asn
20 25 30

Ala Val Ser Ser Glu Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro
35 40 45

Ser Lys Ser Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu
50 55 60

Asp Asp Asp Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp
65 70 75 80

Ser Asp Asp Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser
85 90 95

His His Ser Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp
100 105 110

Leu Pro Ala Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr
115 120 125

Tyr Asp Gly Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser
130 135 140

Lys Lys Phe Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu
145 150 155 160

Asp Ile Thr Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys
165 170 175

Ala Ile Pro Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser
180 185 190

Arg Gly Lys Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala
195 200 205

Glu Thr His Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn
210 215 220

Asp Glu Ser Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser
225 230 235 240

Lys Val Ser Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp
245 250 255

Met Leu Val Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys
260 265 270

Phe Arg Ile Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
275 280 285

<210> SEQ ID NO 63
<211> LENGTH: 411
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

Met Val Cys Phe Arg Leu Phe Pro Val Pro Gly Ser Gly Leu Val Leu
1 5 10 15

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Val Cys Leu Val Leu Gly Ala Val Arg Ser Tyr Ala Leu Glu Leu Asn
            20                  25                  30

Leu Thr Asp Ser Glu Asn Ala Thr Cys Leu Tyr Ala Lys Trp Gln Met
        35                  40                  45

Asn Phe Thr Val Arg Tyr Glu Thr Thr Asn Lys Thr Tyr Lys Thr Val
    50                  55                  60

Thr Ile Ser Asp His Gly Thr Val Thr Tyr Asn Gly Ser Ile Cys Gly
65                  70                  75                  80

Asp Asp Gln Asn Gly Pro Lys Ile Ala Val Gln Phe Gly Pro Gly Phe
                85                  90                  95

Ser Trp Ile Ala Asn Phe Thr Lys Ala Ala Ser Thr Tyr Ser Ile Asp
            100                 105                 110

Ser Val Ser Phe Ser Tyr Asn Thr Gly Asp Asn Thr Thr Phe Pro Asp
        115                 120                 125

Ala Glu Asp Lys Gly Ile Leu Thr Val Asp Glu Leu Leu Ala Ile Arg
    130                 135                 140

Ile Pro Leu Asn Asp Leu Phe Arg Cys Asn Ser Leu Ser Thr Leu Glu
145                 150                 155                 160

Lys Asn Asp Val Val Gln His Tyr Trp Asp Val Leu Val Gln Ala Phe
                165                 170                 175

Val Gln Asn Gly Thr Val Ser Thr Asn Glu Phe Leu Cys Asp Lys Asp
            180                 185                 190

Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro
        195                 200                 205

Thr Thr Thr Pro Thr Pro Lys Glu Lys Pro Glu Ala Gly Thr Tyr Ser
    210                 215                 220

Val Asn Asn Gly Asn Asp Thr Cys Leu Leu Ala Thr Met Gly Leu Gln
225                 230                 235                 240

Leu Asn Ile Thr Gln Asp Lys Val Ala Ser Val Ile Asn Ile Asn Pro
                245                 250                 255

Asn Thr Thr His Ser Thr Gly Ser Cys Arg Ser His Thr Ala Leu Leu
            260                 265                 270

Arg Leu Asn Ser Ser Thr Ile Lys Tyr Leu Asp Phe Val Phe Ala Val
        275                 280                 285

Lys Asn Glu Asn Arg Phe Tyr Leu Lys Glu Val Asn Ile Ser Met Tyr
    290                 295                 300

Leu Val Asn Gly Ser Val Phe Ser Ile Ala Asn Asn Asn Leu Ser Tyr
305                 310                 315                 320

Trp Asp Ala Pro Leu Gly Ser Ser Tyr Met Cys Asn Lys Glu Gln Thr
                325                 330                 335

Val Ser Val Ser Gly Ala Phe Gln Ile Asn Thr Phe Asp Leu Arg Val
            340                 345                 350

Gln Pro Phe Asn Val Thr Gln Gly Lys Tyr Ser Thr Ala Glu Glu Cys
        355                 360                 365

Ser Ala Asp Ser Asp Leu Asn Phe Leu Ile Pro Val Ala Val Gly Val
    370                 375                 380

Ala Leu Gly Phe Leu Ile Ile Val Val Phe Ile Ser Tyr Met Ile Gly
385                 390                 395                 400

Arg Arg Lys Ser Arg Thr Gly Tyr Gln Ser Val
                405                 410
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<210> SEQ ID NO 64
<211> LENGTH: 410

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

Met Val Cys Phe Arg Leu Phe Pro Val Pro Gly Ser Gly Leu Val Leu
1 5 10 15

Val Cys Leu Val Leu Gly Ala Val Arg Ser Tyr Ala Leu Glu Leu Asn
20 25 30

Leu Thr Asp Ser Glu Asn Ala Thr Cys Leu Tyr Ala Lys Trp Gln Met
35 40 45

Asn Phe Thr Val Arg Tyr Glu Thr Thr Asn Lys Thr Tyr Lys Thr Val
50 55 60

Thr Ile Ser Asp His Gly Thr Val Thr Tyr Asn Gly Ser Ile Cys Gly
65 70 75 80

Asp Asp Gln Asn Gly Pro Lys Ile Ala Val Gln Phe Gly Pro Gly Phe
85 90 95

Ser Trp Ile Ala Asn Phe Thr Lys Ala Ala Ser Thr Tyr Ser Ile Asp
100 105 110

Ser Val Ser Phe Ser Tyr Asn Thr Gly Asp Asn Thr Thr Phe Pro Asp
115 120 125

Ala Glu Asp Lys Gly Ile Leu Thr Val Asp Glu Leu Leu Ala Ile Arg
130 135 140

Ile Pro Leu Asn Asp Leu Phe Arg Cys Asn Ser Leu Ser Thr Leu Glu
145 150 155 160

Lys Asn Asp Val Val Gln His Tyr Trp Asp Val Leu Val Gln Ala Phe
165 170 175

Val Gln Asn Gly Thr Val Ser Thr Asn Glu Phe Leu Cys Asp Lys Asp
180 185 190

Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro
195 200 205

Thr Thr Thr Pro Thr Pro Lys Glu Lys Pro Glu Ala Gly Thr Tyr Ser
210 215 220

Val Asn Asn Gly Asn Asp Thr Cys Leu Leu Ala Thr Met Gly Leu Gln
225 230 235 240

Leu Asn Ile Thr Gln Asp Lys Val Ala Ser Val Ile Asn Ile Asn Pro
245 250 255

Asn Thr Thr His Ser Thr Gly Ser Cys Arg Ser His Thr Ala Leu Leu
260 265 270

Arg Leu Asn Ser Ser Thr Ile Lys Tyr Leu Asp Phe Val Phe Ala Val
275 280 285

Lys Asn Glu Asn Arg Phe Tyr Leu Lys Glu Val Asn Ile Ser Met Tyr
290 295 300

Leu Val Asn Gly Ser Val Phe Ser Ile Ala Asn Asn Asn Leu Ser Tyr
305 310 315 320

Trp Asp Ala Pro Leu Gly Ser Ser Tyr Met Cys Asn Lys Glu Gln Thr
325 330 335

Val Ser Val Ser Gly Ala Phe Gln Ile Asn Thr Phe Asp Leu Arg Val
340 345 350

Gln Pro Phe Asn Val Thr Gln Gly Lys Tyr Ser Thr Ala Gln Asp Cys
355 360 365

Ser Ala Asp Asp Asp Asn Phe Leu Val Pro Ile Ala Val Gly Ala Ala
370 375 380

Leu Ala Gly Val Leu Ile Leu Val Leu Leu Ala Tyr Phe Ile Gly Leu
385 390 395 400

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Lys His His His Ala Gly Tyr Glu Gln Phe
405 410

<210> SEQ ID NO 65
<211> LENGTH: 410
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

Met Val Cys Phe Arg Leu Phe Pro Val Pro Gly Ser Gly Leu Val Leu
1 5 10 15

Val Cys Leu Val Leu Gly Ala Val Arg Ser Tyr Ala Leu Glu Leu Asn
20 25 30

Leu Thr Asp Ser Glu Asn Ala Thr Cys Leu Tyr Ala Lys Trp Gln Met
35 40 45

Asn Phe Thr Val Arg Tyr Glu Thr Thr Asn Lys Thr Tyr Lys Thr Val
50 55 60

Thr Ile Ser Asp His Gly Thr Val Thr Tyr Asn Gly Ser Ile Cys Gly
65 70 75 80

Asp Asp Gln Asn Gly Pro Lys Ile Ala Val Gln Phe Gly Pro Gly Phe
85 90 95

Ser Trp Ile Ala Asn Phe Thr Lys Ala Ala Ser Thr Tyr Ser Ile Asp
100 105 110

Ser Val Ser Phe Ser Tyr Asn Thr Gly Asp Asn Thr Thr Phe Pro Asp
115 120 125

Ala Glu Asp Lys Gly Ile Leu Thr Val Asp Glu Leu Leu Ala Ile Arg
130 135 140

Ile Pro Leu Asn Asp Leu Phe Arg Cys Asn Ser Leu Ser Thr Leu Glu
145 150 155 160

Lys Asn Asp Val Val Gln His Tyr Trp Asp Val Leu Val Gln Ala Phe
165 170 175

Val Gln Asn Gly Thr Val Ser Thr Asn Glu Phe Leu Cys Asp Lys Asp
180 185 190

Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro
195 200 205

Thr Thr Thr Pro Thr Pro Lys Glu Lys Pro Glu Ala Gly Thr Tyr Ser
210 215 220

Val Asn Asn Gly Asn Asp Thr Cys Leu Leu Ala Thr Met Gly Leu Gln
225 230 235 240

Leu Asn Ile Thr Gln Asp Lys Val Ala Ser Val Ile Asn Ile Asn Pro
245 250 255

Asn Thr Thr His Ser Thr Gly Ser Cys Arg Ser His Thr Ala Leu Leu
260 265 270

Arg Leu Asn Ser Ser Thr Ile Lys Tyr Leu Asp Phe Val Phe Ala Val
275 280 285

Lys Asn Glu Asn Arg Phe Tyr Leu Lys Glu Val Asn Ile Ser Met Tyr
290 295 300

Leu Val Asn Gly Ser Val Phe Ser Ile Ala Asn Asn Asn Leu Ser Tyr
305 310 315 320

Trp Asp Ala Pro Leu Gly Ser Ser Tyr Met Cys Asn Lys Glu Gln Thr
325 330 335

Val Ser Val Ser Gly Ala Phe Gln Ile Asn Thr Phe Asp Leu Arg Val
340 345 350

Gln Pro Phe Asn Val Thr Gln Gly Lys Tyr Ser Thr Ala Gln Glu Cys

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        355                 360                 365

Ser Leu Asp Asp Asp Thr Ile Leu Ile Pro Ile Ile Val Gly Ala Gly
    370                 375                 380

Leu Ser Gly Leu Ile Ile Val Ile Val Ile Ala Tyr Val Ile Gly Arg
385                 390                 395                 400

Arg Lys Ser Tyr Ala Gly Tyr Gln Thr Leu
                405                 410


<210> SEQ ID NO 66
<211> LENGTH: 262
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

Met Trp Phe Leu Val Leu Cys Leu Ala Leu Ser Leu Gly Gly Thr Gly
1               5                   10                  15

Ala Ala Pro Pro Ile Gln Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
            20                  25                  30

Gln His Ser Gln Pro Trp Gln Ala Ala Leu Tyr His Phe Ser Thr Phe
        35                  40                  45

Gln Cys Gly Gly Ile Leu Val His Arg Gln Trp Val Leu Thr Ala Ala
    50                  55                  60

His Cys Ile Ser Asp Asn Tyr Gln Leu Trp Leu Gly Arg His Asn Leu
65                  70                  75                  80

Phe Asp Asp Glu Asn Thr Ala Gln Phe Val His Val Ser Glu Ser Phe
                85                  90                  95

Pro His Pro Gly Phe Asn Met Ser Leu Leu Glu Asn His Thr Arg Gln
            100                 105                 110

Ala Asp Glu Asp Tyr Ser His Asp Leu Met Leu Leu Arg Leu Thr Glu
        115                 120                 125

Pro Ala Asp Thr Ile Thr Asp Ala Val Lys Val Val Glu Leu Pro Thr
    130                 135                 140

Glu Glu Pro Glu Val Gly Ser Thr Cys Leu Ala Ser Gly Trp Gly Ser
145                 150                 155                 160

Ile Glu Pro Glu Asn Phe Ser Phe Pro Asp Asp Leu Gln Cys Val Asp
                165                 170                 175

Leu Lys Ile Leu Pro Asn Asp Glu Cys Lys Lys Ala His Val Gln Lys
            180                 185                 190

Val Thr Asp Phe Met Leu Cys Val Gly His Leu Glu Gly Gly Lys Asp
        195                 200                 205

Thr Cys Val Gly Asp Ser Gly Gly Pro Leu Met Cys Asp Gly Val Leu
    210                 215                 220

Gln Gly Val Thr Ser Trp Gly Tyr Val Pro Cys Gly Thr Pro Asn Lys
225                 230                 235                 240

Pro Ser Val Ala Val Arg Val Leu Ser Tyr Val Lys Trp Ile Glu Asp
                245                 250                 255

Thr Ile Ala Glu Asn Ser
            260


<210> SEQ ID NO 67
<211> LENGTH: 860
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

Met Gly Pro Trp Gly Trp Lys Leu Arg Trp Thr Val Ala Leu Leu Leu
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1               5                   10                  15

Ala Ala Ala Gly Thr Ala Val Gly Asp Arg Cys Glu Arg Asn Glu Phe
            20                  25                  30

Gln Cys Gln Asp Gly Lys Cys Ile Ser Tyr Lys Trp Val Cys Asp Gly
        35                  40                  45

Ser Ala Glu Cys Gln Asp Gly Ser Asp Glu Ser Gln Glu Thr Cys Leu
    50                  55                  60

Ser Val Thr Cys Lys Ser Gly Asp Phe Ser Cys Gly Gly Arg Val Asn
65                  70                  75                  80

Arg Cys Ile Pro Gln Phe Trp Arg Cys Asp Gly Gln Val Asp Cys Asp
                85                  90                  95

Asn Gly Ser Asp Glu Gln Gly Cys Pro Pro Lys Thr Cys Ser Gln Asp
            100                 105                 110

Glu Phe Arg Cys His Asp Gly Lys Cys Ile Ser Arg Gln Phe Val Cys
        115                 120                 125

Asp Ser Asp Arg Asp Cys Leu Asp Gly Ser Asp Glu Ala Ser Cys Pro
    130                 135                 140

Val Leu Thr Cys Gly Pro Ala Ser Phe Gln Cys Asn Ser Ser Thr Cys
145                 150                 155                 160

Ile Pro Gln Leu Trp Ala Cys Asp Asn Asp Pro Asp Cys Glu Asp Gly
                165                 170                 175

Ser Asp Glu Trp Pro Gln Arg Cys Arg Gly Leu Tyr Val Phe Gln Gly
            180                 185                 190

Asp Ser Ser Pro Cys Ser Ala Phe Glu Phe His Cys Leu Ser Gly Glu
        195                 200                 205

Cys Ile His Ser Ser Trp Arg Cys Asp Gly Gly Pro Asp Cys Lys Asp
    210                 215                 220

Lys Ser Asp Glu Glu Asn Cys Ala Val Ala Thr Cys Arg Pro Asp Glu
225                 230                 235                 240

Phe Gln Cys Ser Asp Gly Asn Cys Ile His Gly Ser Arg Gln Cys Asp
                245                 250                 255

Arg Glu Tyr Asp Cys Lys Asp Met Ser Asp Glu Val Gly Cys Val Asn
            260                 265                 270

Val Thr Leu Cys Glu Gly Pro Asn Lys Phe Lys Cys His Ser Gly Glu
        275                 280                 285

Cys Ile Thr Leu Asp Lys Val Cys Asn Met Ala Arg Asp Cys Arg Asp
    290                 295                 300

Trp Ser Asp Glu Pro Ile Lys Glu Cys Gly Thr Asn Glu Cys Leu Asp
305                 310                 315                 320

Asn Asn Gly Gly Cys Ser His Val Cys Asn Asp Leu Lys Ile Gly Tyr
                325                 330                 335

Glu Cys Leu Cys Pro Asp Gly Phe Gln Leu Val Ala Gln Arg Arg Cys
            340                 345                 350

Glu Asp Ile Asp Glu Cys Gln Asp Pro Asp Thr Cys Ser Gln Leu Cys
        355                 360                 365

Val Asn Leu Glu Gly Gly Tyr Lys Cys Gln Cys Glu Glu Gly Phe Gln
    370                 375                 380

Leu Asp Pro His Thr Lys Ala Cys Lys Ala Val Gly Ser Ile Ala Tyr
385                 390                 395                 400

Leu Phe Phe Thr Asn Arg His Glu Val Arg Lys Met Thr Leu Asp Arg
                405                 410                 415

Ser Glu Tyr Thr Ser Leu Ile Pro Asn Leu Arg Asn Val Val Ala Leu
            420                 425                 430
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Asp Thr Glu Val Ala Ser Asn Arg Ile Tyr Trp Ser Asp Leu Ser Gln
        435                 440                 445

Arg Met Ile Cys Ser Thr Gln Leu Asp Arg Ala His Gly Val Ser Ser
    450                 455                 460

Tyr Asp Thr Val Ile Ser Arg Asp Ile Gln Ala Pro Asp Gly Leu Ala
465                 470                 475                 480

Val Asp Trp Ile His Ser Asn Ile Tyr Trp Thr Asp Ser Val Leu Gly
                485                 490                 495

Thr Val Ser Val Ala Asp Thr Lys Gly Val Lys Arg Lys Thr Leu Phe
            500                 505                 510

Arg Glu Asn Gly Ser Lys Pro Arg Ala Ile Val Val Asp Pro Val His
        515                 520                 525

Gly Phe Met Tyr Trp Thr Asp Trp Gly Thr Pro Ala Lys Ile Lys Lys
    530                 535                 540

Gly Gly Leu Asn Gly Val Asp Ile Tyr Ser Leu Val Thr Glu Asn Ile
545                 550                 555                 560

Gln Trp Pro Asn Gly Ile Thr Leu Asp Leu Leu Ser Gly Arg Leu Tyr
                565                 570                 575

Trp Val Asp Ser Lys Leu His Ser Ile Ser Ser Ile Asp Val Asn Gly
            580                 585                 590

Gly Asn Arg Lys Thr Ile Leu Glu Asp Glu Lys Arg Leu Ala His Pro
        595                 600                 605

Phe Ser Leu Ala Val Phe Glu Asp Lys Val Phe Trp Thr Asp Ile Ile
    610                 615                 620

Asn Glu Ala Ile Phe Ser Ala Asn Arg Leu Thr Gly Ser Asp Val Asn
625                 630                 635                 640

Leu Leu Ala Glu Asn Leu Leu Ser Pro Glu Asp Met Val Leu Phe His
                645                 650                 655

Asn Leu Thr Gln Pro Arg Gly Val Asn Trp Cys Glu Arg Thr Thr Leu
            660                 665                 670

Ser Asn Gly Gly Cys Gln Tyr Leu Cys Leu Pro Ala Pro Gln Ile Asn
        675                 680                 685

Pro His Ser Pro Lys Phe Thr Cys Ala Cys Pro Asp Gly Met Leu Leu
    690                 695                 700

Ala Arg Asp Met Arg Ser Cys Leu Thr Glu Ala Glu Ala Ala Val Ala
705                 710                 715                 720

Thr Gln Glu Thr Ser Thr Val Arg Leu Lys Val Ser Ser Thr Ala Val
                725                 730                 735

Arg Thr Gln His Thr Thr Thr Arg Pro Val Pro Asp Thr Ser Arg Leu
            740                 745                 750

Pro Gly Ala Thr Pro Gly Leu Thr Thr Val Glu Ile Val Thr Met Ser
        755                 760                 765

His Gln Ala Leu Gly Asp Val Ala Gly Arg Gly Asn Glu Lys Lys Pro
    770                 775                 780

Ser Ser Val Arg Ala Leu Ser Ile Val Leu Pro Ile Val Leu Leu Val
785                 790                 795                 800

Phe Leu Cys Leu Gly Val Phe Leu Leu Trp Lys Asn Trp Arg Leu Lys
                805                 810                 815

Asn Ile Asn Ser Ile Asn Phe Asp Asn Pro Val Tyr Gln Lys Thr Thr
            820                 825                 830

Glu Asp Glu Val His Ile Cys His Asn Gln Asp Gly Tyr Ser Tyr Pro
        835                 840                 845
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Ser Arg Gln Met Val Ser Leu Glu Asp Asp Val Ala
    850                 855                 860


<210> SEQ ID NO 68
<211> LENGTH: 800
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

Met Gly Thr Ser Ala Leu Trp Ala Leu Trp Leu Leu Leu Ala Leu Cys
1               5                   10                  15

Trp Ala Pro Arg Glu Ser Gly Ala Thr Gly Thr Gly Arg Lys Ala Lys
            20                  25                  30

Cys Glu Pro Ser Gln Phe Gln Cys Thr Asn Gly Arg Cys Ile Thr Leu
        35                  40                  45

Leu Trp Lys Cys Asp Gly Asp Glu Asp Cys Val Asp Gly Ser Asp Glu
    50                  55                  60

Lys Asn Cys Val Lys Lys Thr Cys Ala Glu Ser Asp Phe Val Cys Asn
65                  70                  75                  80

Asn Gly Gln Cys Val Pro Ser Arg Trp Lys Cys Asp Gly Asp Pro Asp
                85                  90                  95

Cys Glu Asp Gly Ser Asp Glu Ser Pro Glu Gln Cys His Met Arg Thr
            100                 105                 110

Cys Arg Ile His Glu Ile Ser Cys Gly Ala His Ser Thr Gln Cys Ile
        115                 120                 125

Pro Val Ser Trp Arg Cys Asp Gly Glu Asn Asp Cys Asp Ser Gly Glu
    130                 135                 140

Asp Glu Glu Asn Cys Gly Asn Ile Thr Cys Ser Pro Asp Glu Phe Thr
145                 150                 155                 160

Cys Ser Ser Gly Arg Cys Ile Ser Arg Asn Phe Val Cys Asn Gly Gln
                165                 170                 175

Asp Asp Cys Ser Asp Gly Ser Asp Glu Leu Asp Cys Ala Pro Pro Thr
            180                 185                 190

Cys Gly Ala His Glu Phe Gln Cys Ser Thr Ser Ser Cys Ile Pro Ile
        195                 200                 205

Ser Trp Val Cys Asp Asp Asp Ala Asp Cys Ser Asp Gln Ser Asp Glu
    210                 215                 220

Ser Leu Glu Gln Cys Gly Arg Gln Pro Val Ile His Thr Lys Cys Pro
225                 230                 235                 240

Ala Ser Glu Ile Gln Cys Gly Ser Gly Glu Cys Ile His Lys Lys Trp
                245                 250                 255

Arg Cys Asp Gly Asp Pro Asp Cys Lys Asp Gly Ser Asp Glu Val Asn
            260                 265                 270

Cys Pro Ser Arg Thr Cys Arg Pro Asp Gln Phe Glu Cys Glu Asp Gly
        275                 280                 285

Ser Cys Ile His Gly Ser Arg Gln Cys Asn Gly Ile Arg Asp Cys Val
    290                 295                 300

Asp Gly Ser Asp Glu Val Asn Cys Lys Asn Val Asn Gln Cys Leu Gly
305                 310                 315                 320

Pro Gly Lys Phe Lys Cys Arg Ser Gly Glu Cys Ile Asp Ile Ser Lys
                325                 330                 335

Val Cys Asn Gln Glu Gln Asp Cys Arg Asp Trp Ser Asp Glu Pro Leu
            340                 345                 350

Lys Glu Cys His Ile Asn Glu Cys Leu Val Asn Asn Gly Gly Cys Ser
        355                 360                 365
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His Ile Cys Lys Asp Leu Val Ile Gly Tyr Glu Cys Asp Cys Ala Ala
    370                 375                 380

Gly Phe Glu Leu Ile Asp Arg Lys Thr Cys Gly Asp Ile Asp Glu Cys
385                 390                 395                 400

Gln Asn Pro Gly Ile Cys Ser Gln Ile Cys Ile Asn Leu Lys Gly Gly
                405                 410                 415

Tyr Lys Cys Glu Cys Ser Arg Gly Tyr Gln Met Asp Leu Ala Thr Gly
            420                 425                 430

Val Cys Lys Ala Val Gly Lys Glu Pro Ser Leu Ile Phe Thr Asn Arg
        435                 440                 445

Arg Asp Ile Arg Lys Ile Gly Leu Glu Arg Lys Glu Tyr Ile Gln Leu
    450                 455                 460

Val Glu Gln Leu Arg Asn Thr Val Ala Leu Asp Ala Asp Ile Ala Ala
465                 470                 475                 480

Gln Lys Leu Phe Trp Ala Asp Leu Ser Gln Lys Ala Ile Phe Ser Ala
                485                 490                 495

Ser Ile Asp Asp Lys Val Gly Arg His Val Lys Met Ile Asp Asn Val
            500                 505                 510

Tyr Asn Pro Ala Ala Ile Ala Val Asp Trp Val Tyr Lys Thr Ile Tyr
        515                 520                 525

Trp Thr Asp Ala Ala Ser Lys Thr Ile Ser Val Ala Thr Leu Asp Gly
    530                 535                 540

Thr Lys Arg Lys Phe Leu Phe Asn Ser Asp Leu Arg Glu Pro Ala Ser
545                 550                 555                 560

Ile Ala Val Asp Pro Leu Ser Gly Phe Val Tyr Trp Ser Asp Trp Gly
                565                 570                 575

Glu Pro Ala Lys Ile Glu Lys Ala Gly Met Asn Gly Phe Asp Arg Arg
            580                 585                 590

Pro Leu Val Thr Ala Asp Ile Gln Trp Pro Asn Gly Ile Thr Leu Asp
        595                 600                 605

Leu Ile Lys Ser Arg Leu Tyr Trp Leu Asp Ser Lys Leu His Met Leu
    610                 615                 620

Ser Ser Val Asp Leu Asn Gly Gln Asp Arg Arg Ile Val Leu Lys Ser
625                 630                 635                 640

Leu Glu Phe Leu Ala His Pro Leu Ala Leu Thr Ile Phe Glu Asp Arg
                645                 650                 655

Val Tyr Trp Ile Asp Gly Glu Asn Glu Ala Val Tyr Gly Ala Asn Lys
            660                 665                 670

Phe Thr Gly Ser Glu Leu Ala Thr Leu Val Asn Asn Leu Asn Asp Ala
        675                 680                 685

Gln Asp Ile Ile Val Tyr His Glu Leu Val Gln Pro Ser Gly Lys Asn
    690                 695                 700

Trp Cys Glu Glu Asp Met Glu Asn Gly Gly Cys Glu Tyr Leu Cys Leu
705                 710                 715                 720

Pro Ala Pro Gln Ile Asn Asp His Ser Pro Lys Tyr Thr Cys Ser Cys
                725                 730                 735

Pro Ser Gly Tyr Asn Val Glu Glu Asn Gly Arg Asp Cys Gln Arg Ile
            740                 745                 750

Asn Val Thr Thr Ala Val Ser Glu Val Ser Val Pro Pro Lys Gly Thr
        755                 760                 765

Ser Ala Ala Trp Ala Ile Leu Pro Leu Leu Leu Leu Val Met Ala Ala
    770                 775                 780
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Val Gly Gly Tyr Leu Met Trp Arg Asn Trp Gln His Lys Asn Met Lys
785                 790                 795                 800


<210> SEQ ID NO 69
<211> LENGTH: 873
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

Met Gly Thr Ser Ala Leu Trp Ala Leu Trp Leu Leu Leu Ala Leu Cys
1               5                   10                  15

Trp Ala Pro Arg Glu Ser Gly Ala Thr Gly Thr Gly Arg Lys Ala Lys
            20                  25                  30

Cys Glu Pro Ser Gln Phe Gln Cys Thr Asn Gly Arg Cys Ile Thr Leu
        35                  40                  45

Leu Trp Lys Cys Asp Gly Asp Glu Asp Cys Val Asp Gly Ser Asp Glu
    50                  55                  60

Lys Asn Cys Val Lys Lys Thr Cys Ala Glu Ser Asp Phe Val Cys Asn
65                  70                  75                  80

Asn Gly Gln Cys Val Pro Ser Arg Trp Lys Cys Asp Gly Asp Pro Asp
                85                  90                  95

Cys Glu Asp Gly Ser Asp Glu Ser Pro Glu Gln Cys His Met Arg Thr
            100                 105                 110

Cys Arg Ile His Glu Ile Ser Cys Gly Ala His Ser Thr Gln Cys Ile
        115                 120                 125

Pro Val Ser Trp Arg Cys Asp Gly Glu Asn Asp Cys Asp Ser Gly Glu
    130                 135                 140

Asp Glu Glu Asn Cys Gly Asn Ile Thr Cys Ser Pro Asp Glu Phe Thr
145                 150                 155                 160

Cys Ser Ser Gly Arg Cys Ile Ser Arg Asn Phe Val Cys Asn Gly Gln
                165                 170                 175

Asp Asp Cys Ser Asp Gly Ser Asp Glu Leu Asp Cys Ala Pro Pro Thr
            180                 185                 190

Cys Gly Ala His Glu Phe Gln Cys Ser Thr Ser Ser Cys Ile Pro Ile
        195                 200                 205

Ser Trp Val Cys Asp Asp Asp Ala Asp Cys Ser Asp Gln Ser Asp Glu
    210                 215                 220

Ser Leu Glu Gln Cys Gly Arg Gln Pro Val Ile His Thr Lys Cys Pro
225                 230                 235                 240

Ala Ser Glu Ile Gln Cys Gly Ser Gly Glu Cys Ile His Lys Lys Trp
                245                 250                 255

Arg Cys Asp Gly Asp Pro Asp Cys Lys Asp Gly Ser Asp Glu Val Asn
            260                 265                 270

Cys Pro Ser Arg Thr Cys Arg Pro Asp Gln Phe Glu Cys Glu Asp Gly
        275                 280                 285

Ser Cys Ile His Gly Ser Arg Gln Cys Asn Gly Ile Arg Asp Cys Val
    290                 295                 300

Asp Gly Ser Asp Glu Val Asn Cys Lys Asn Val Asn Gln Cys Leu Gly
305                 310                 315                 320

Pro Gly Lys Phe Lys Cys Arg Ser Gly Glu Cys Ile Asp Ile Ser Lys
                325                 330                 335

Val Cys Asn Gln Glu Gln Asp Cys Arg Asp Trp Ser Asp Glu Pro Leu
            340                 345                 350

Lys Glu Cys His Ile Asn Glu Cys Leu Val Asn Asn Gly Gly Cys Ser
        355                 360                 365
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```
His Ile Cys Lys Asp Leu Val Ile Gly Tyr Glu Cys Asp Cys Ala Ala
    370                 375                 380

Gly Phe Glu Leu Ile Asp Arg Lys Thr Cys Gly Asp Ile Asp Glu Cys
385                 390                 395                 400

Gln Asn Pro Gly Ile Cys Ser Gln Ile Cys Ile Asn Leu Lys Gly Gly
                405                 410                 415

Tyr Lys Cys Glu Cys Ser Arg Gly Tyr Gln Met Asp Leu Ala Thr Gly
            420                 425                 430

Val Cys Lys Ala Val Gly Lys Glu Pro Ser Leu Ile Phe Thr Asn Arg
        435                 440                 445

Arg Asp Ile Arg Lys Ile Gly Leu Glu Arg Lys Glu Tyr Ile Gln Leu
    450                 455                 460

Val Glu Gln Leu Arg Asn Thr Val Ala Leu Asp Ala Asp Ile Ala Ala
465                 470                 475                 480

Gln Lys Leu Phe Trp Ala Asp Leu Ser Gln Lys Ala Ile Phe Ser Ala
                485                 490                 495

Ser Ile Asp Asp Lys Val Gly Arg His Val Lys Met Ile Asp Asn Val
            500                 505                 510

Tyr Asn Pro Ala Ala Ile Ala Val Asp Trp Val Tyr Lys Thr Ile Tyr
        515                 520                 525

Trp Thr Asp Ala Ala Ser Lys Thr Ile Ser Val Ala Thr Leu Asp Gly
    530                 535                 540

Thr Lys Arg Lys Phe Leu Phe Asn Ser Asp Leu Arg Glu Pro Ala Ser
545                 550                 555                 560

Ile Ala Val Asp Pro Leu Ser Gly Phe Val Tyr Trp Ser Asp Trp Gly
                565                 570                 575

Glu Pro Ala Lys Ile Glu Lys Ala Gly Met Asn Gly Phe Asp Arg Arg
            580                 585                 590

Pro Leu Val Thr Ala Asp Ile Gln Trp Pro Asn Gly Ile Thr Leu Asp
        595                 600                 605

Leu Ile Lys Ser Arg Leu Tyr Trp Leu Asp Ser Lys Leu His Met Leu
    610                 615                 620

Ser Ser Val Asp Leu Asn Gly Gln Asp Arg Arg Ile Val Leu Lys Ser
625                 630                 635                 640

Leu Glu Phe Leu Ala His Pro Leu Ala Leu Thr Ile Phe Glu Asp Arg
                645                 650                 655

Val Tyr Trp Ile Asp Gly Glu Asn Glu Ala Val Tyr Gly Ala Asn Lys
            660                 665                 670

Phe Thr Gly Ser Glu Leu Ala Thr Leu Val Asn Asn Leu Asn Asp Ala
        675                 680                 685

Gln Asp Ile Ile Val Tyr His Glu Leu Val Gln Pro Ser Gly Lys Asn
    690                 695                 700

Trp Cys Glu Glu Asp Met Glu Asn Gly Gly Cys Glu Tyr Leu Cys Leu
705                 710                 715                 720

Pro Ala Pro Gln Ile Asn Asp His Ser Pro Lys Tyr Thr Cys Ser Cys
                725                 730                 735

Pro Ser Gly Tyr Asn Val Glu Glu Asn Gly Arg Asp Cys Gln Ser Thr
            740                 745                 750

Ala Thr Thr Val Thr Tyr Ser Glu Thr Lys Asp Thr Asn Thr Thr Glu
        755                 760                 765

Ile Ser Ala Thr Ser Gly Leu Val Pro Gly Gly Ile Asn Val Thr Thr
    770                 775                 780
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```
Ala Val Ser Glu Val Ser Val Pro Pro Lys Gly Thr Ser Ala Ala Trp
785                 790                 795                 800

Ala Ile Leu Pro Leu Leu Leu Leu Val Met Ala Ala Val Gly Gly Tyr
                805                 810                 815

Leu Met Trp Arg Asn Trp Gln His Lys Asn Met Lys Ser Met Asn Phe
            820                 825                 830

Asp Asn Pro Val Tyr Leu Lys Thr Thr Glu Glu Asp Leu Ser Ile Asp
        835                 840                 845

Ile Gly Arg His Ser Ala Ser Val Gly His Thr Tyr Pro Ala Ile Ser
    850                 855                 860

Val Val Ser Thr Asp Asp Asp Leu Ala
865                 870


<210> SEQ ID NO 70
<211> LENGTH: 1255
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
1               5                   10                  15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
            20                  25                  30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
        35                  40                  45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
    50                  55                  60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65                  70                  75                  80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
                85                  90                  95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
            100                 105                 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
        115                 120                 125

Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
    130                 135                 140

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145                 150                 155                 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
                165                 170                 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
            180                 185                 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
        195                 200                 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
    210                 215                 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225                 230                 235                 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
                245                 250                 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
            260                 265                 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
        275                 280                 285
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```
Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
    290                 295                 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305                 310                 315                 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
                325                 330                 335

Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu
            340                 345                 350

Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys
        355                 360                 365

Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp
    370                 375                 380

Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe
385                 390                 395                 400

Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro
                405                 410                 415

Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg
            420                 425                 430

Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu
        435                 440                 445

Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly
    450                 455                 460

Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val
465                 470                 475                 480

Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr
                485                 490                 495

Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His
            500                 505                 510

Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys
        515                 520                 525

Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys
    530                 535                 540

Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys
545                 550                 555                 560

Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys
                565                 570                 575

Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp
            580                 585                 590

Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu
        595                 600                 605

Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln
    610                 615                 620

Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys
625                 630                 635                 640

Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile Ile Ser
                645                 650                 655

Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val Phe Gly
            660                 665                 670

Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg
        675                 680                 685

Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly
    690                 695                 700
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```
Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu Leu
705                 710                 715                 720

Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys
                725                 730                 735

Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala Ile
            740                 745                 750

Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu
        755                 760                 765

Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser Arg
    770                 775                 780

Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln Leu
785                 790                 795                 800

Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn Arg Gly Arg
                805                 810                 815

Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala Lys Gly
            820                 825                 830

Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu Ala Ala
        835                 840                 845

Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe
    850                 855                 860

Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp
865                 870                 875                 880

Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg
                885                 890                 895

Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val
            900                 905                 910

Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala
        915                 920                 925

Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro
    930                 935                 940

Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met
945                 950                 955                 960

Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe
                965                 970                 975

Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu
            980                 985                 990

Asp Leu Gly Pro Ala Ser Pro Leu  Asp Ser Thr Phe Tyr  Arg Ser Leu
        995                 1000                1005

Leu Glu  Asp Asp Asp Met Gly  Asp Leu Val Asp Ala  Glu Glu Tyr
    1010                1015                1020

Leu Val  Pro Gln Gln Gly Phe  Phe Cys Pro Asp Pro  Ala Pro Gly
    1025                1030                1035

Ala Gly  Gly Met Val His His  Arg His Arg Ser Ser  Ser Thr Arg
    1040                1045                1050

Ser Gly  Gly Gly Asp Leu Thr  Leu Gly Leu Glu Pro  Ser Glu Glu
    1055                1060                1065

Glu Ala  Pro Arg Ser Pro Leu  Ala Pro Ser Glu Gly  Ala Gly Ser
    1070                1075                1080

Asp Val  Phe Asp Gly Asp Leu  Gly Met Gly Ala Ala  Lys Gly Leu
    1085                1090                1095

Gln Ser  Leu Pro Thr His Asp  Pro Ser Pro Leu Gln  Arg Tyr Ser
    1100                1105                1110

Glu Asp  Pro Thr Val Pro Leu  Pro Ser Glu Thr Asp  Gly Tyr Val
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    1115                1120                1125

Ala Pro  Leu Thr Cys Ser Pro  Gln Pro Glu Tyr Val  Asn Gln Pro
    1130                1135                1140

Asp Val  Arg Pro Gln Pro Pro  Ser Pro Arg Glu Gly  Pro Leu Pro
    1145                1150                1155

Ala Ala  Arg Pro Ala Gly Ala  Thr Leu Glu Arg Pro  Lys Thr Leu
    1160                1165                1170

Ser Pro  Gly Lys Asn Gly Val  Val Lys Asp Val Phe  Ala Phe Gly
    1175                1180                1185

Gly Ala  Val Glu Asn Pro Glu  Tyr Leu Thr Pro Gln  Gly Gly Ala
    1190                1195                1200

Ala Pro  Gln Pro His Pro Pro  Pro Ala Phe Ser Pro  Ala Phe Asp
    1205                1210                1215

Asn Leu  Tyr Tyr Trp Asp Gln  Asp Pro Pro Glu Arg  Gly Ala Pro
    1220                1225                1230

Pro Ser  Thr Phe Lys Gly Thr  Pro Thr Ala Glu Asn  Pro Glu Tyr
    1235                1240                1245

Leu Gly  Leu Asp Val Pro Val
    1250                1255


<210> SEQ ID NO 71
<211> LENGTH: 1225
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

Met Lys Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu
1               5                   10                  15

Arg His Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu
            20                  25                  30

Thr Tyr Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln
        35                  40                  45

Glu Val Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val
    50                  55                  60

Pro Leu Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp
65                  70                  75                  80

Asn Tyr Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr
                85                  90                  95

Thr Pro Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu
            100                 105                 110

Arg Ser Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn
        115                 120                 125

Pro Gln Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His
    130                 135                 140

Lys Asn Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg
145                 150                 155                 160

Ala Cys His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly
                165                 170                 175

Glu Ser Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly
            180                 185                 190

Gly Cys Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu
        195                 200                 205

Gln Cys Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala
    210                 215                 220
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```
Cys Leu His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala
225                 230                 235                 240

Leu Val Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu
                245                 250                 255

Gly Arg Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn
            260                 265                 270

Tyr Leu Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His
        275                 280                 285

Asn Gln Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys
    290                 295                 300

Ser Lys Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu
305                 310                 315                 320

Arg Glu Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly
                325                 330                 335

Cys Lys Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp
            340                 345                 350

Gly Asp Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln
        355                 360                 365

Val Phe Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala
    370                 375                 380

Trp Pro Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val
385                 390                 395                 400

Ile Arg Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln
                405                 410                 415

Gly Leu Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly
            420                 425                 430

Ser Gly Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His
        435                 440                 445

Thr Val Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu
    450                 455                 460

His Thr Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala
465                 470                 475                 480

Cys His Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr
                485                 490                 495

Gln Cys Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu
            500                 505                 510

Glu Cys Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg
        515                 520                 525

His Cys Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val
    530                 535                 540

Thr Cys Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr
545                 550                 555                 560

Lys Asp Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro
                565                 570                 575

Asp Leu Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala
            580                 585                 590

Cys Gln Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp
        595                 600                 605

Asp Lys Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile
    610                 615                 620

Ile Ser Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val
625                 630                 635                 640

Phe Gly Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr
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                645                 650                 655

Met Arg Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro
            660                 665                 670

Ser Gly Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr
        675                 680                 685

Glu Leu Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val
    690                 695                 700

Tyr Lys Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val
705                 710                 715                 720

Ala Ile Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu
                725                 730                 735

Ile Leu Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val
            740                 745                 750

Ser Arg Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr
        755                 760                 765

Gln Leu Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn Arg
    770                 775                 780

Gly Arg Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala
785                 790                 795                 800

Lys Gly Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu
                805                 810                 815

Ala Ala Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr
            820                 825                 830

Asp Phe Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His
        835                 840                 845

Ala Asp Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile
    850                 855                 860

Leu Arg Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val
865                 870                 875                 880

Thr Val Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile
                885                 890                 895

Pro Ala Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro
            900                 905                 910

Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys
        915                 920                 925

Trp Met Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser
    930                 935                 940

Glu Phe Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln
945                 950                 955                 960

Asn Glu Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg
                965                 970                 975

Ser Leu Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu
            980                 985                 990

Tyr Leu Val Pro Gln Gln Gly Phe  Phe Cys Pro Asp Pro  Ala Pro Gly
        995                 1000                1005

Ala Gly  Gly Met Val His His  Arg His Arg Ser Ser  Ser Thr Arg
    1010                1015                1020

Ser Gly  Gly Gly Asp Leu Thr  Leu Gly Leu Glu Pro  Ser Glu Glu
    1025                1030                1035

Glu Ala  Pro Arg Ser Pro Leu  Ala Pro Ser Glu Gly  Ala Gly Ser
    1040                1045                1050

Asp Val  Phe Asp Gly Asp Leu  Gly Met Gly Ala Ala  Lys Gly Leu
    1055                1060                1065
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Gln Ser  Leu Pro Thr His Asp  Pro Ser Pro Leu Gln  Arg Tyr Ser
    1070                1075                1080

Glu Asp  Pro Thr Val Pro Leu  Pro Ser Glu Thr Asp  Gly Tyr Val
    1085                1090                1095

Ala Pro  Leu Thr Cys Ser Pro  Gln Pro Glu Tyr Val  Asn Gln Pro
    1100                1105                1110

Asp Val  Arg Pro Gln Pro Pro  Ser Pro Arg Glu Gly  Pro Leu Pro
    1115                1120                1125

Ala Ala  Arg Pro Ala Gly Ala  Thr Leu Glu Arg Pro  Lys Thr Leu
    1130                1135                1140

Ser Pro  Gly Lys Asn Gly Val  Val Lys Asp Val Phe  Ala Phe Gly
    1145                1150                1155

Gly Ala  Val Glu Asn Pro Glu  Tyr Leu Thr Pro Gln  Gly Gly Ala
    1160                1165                1170

Ala Pro  Gln Pro His Pro Pro  Pro Ala Phe Ser Pro  Ala Phe Asp
    1175                1180                1185

Asn Leu  Tyr Tyr Trp Asp Gln  Asp Pro Pro Glu Arg  Gly Ala Pro
    1190                1195                1200

Pro Ser  Thr Phe Lys Gly Thr  Pro Thr Ala Glu Asn  Pro Glu Tyr
    1205                1210                1215

Leu Gly  Leu Asp Val Pro Val
    1220                1225


<210> SEQ ID NO 72
<211> LENGTH: 654
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

Met Lys Leu Ser Leu Val Ala Ala Met Leu Leu Leu Leu Ser Ala Ala
1               5                  10                  15

Arg Ala Glu Glu Glu Asp Lys Lys Glu Asp Val Gly Thr Val Val Gly
            20                  25                  30

Ile Asp Leu Gly Thr Thr Tyr Ser Cys Val Gly Val Phe Lys Asn Gly
        35                  40                  45

Arg Val Glu Ile Ile Ala Asn Asp Gln Gly Asn Arg Ile Thr Pro Ser
    50                  55                  60

Tyr Val Ala Phe Thr Pro Glu Gly Glu Arg Leu Ile Gly Asp Ala Ala
65                  70                  75                  80

Lys Asn Gln Leu Thr Ser Asn Pro Glu Asn Thr Val Phe Asp Ala Lys
                85                  90                  95

Arg Leu Ile Gly Arg Thr Trp Asn Asp Pro Ser Val Gln Gln Asp Ile
            100                 105                 110

Lys Phe Leu Pro Phe Lys Val Val Glu Lys Lys Thr Lys Pro Tyr Ile
        115                 120                 125

Gln Val Asp Ile Gly Gly Gly Gln Thr Lys Thr Phe Ala Pro Glu Glu
    130                 135                 140

Ile Ser Ala Met Val Leu Thr Lys Met Lys Glu Thr Ala Glu Ala Tyr
145                 150                 155                 160

Leu Gly Lys Lys Val Thr His Ala Val Val Thr Val Pro Ala Tyr Phe
                165                 170                 175

Asn Asp Ala Gln Arg Gln Ala Thr Lys Asp Ala Gly Thr Ile Ala Gly
            180                 185                 190

Leu Asn Val Met Arg Ile Ile Asn Glu Pro Thr Ala Ala Ala Ile Ala
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        195                 200                 205

Tyr Gly Leu Asp Lys Arg Glu Gly Glu Lys Asn Ile Leu Val Phe Asp
    210                 215                 220

Leu Gly Gly Gly Thr Phe Asp Val Ser Leu Leu Thr Ile Asp Asn Gly
225                 230                 235                 240

Val Phe Glu Val Val Ala Thr Asn Gly Asp Thr His Leu Gly Gly Glu
                245                 250                 255

Asp Phe Asp Gln Arg Val Met Glu His Phe Ile Lys Leu Tyr Lys Lys
            260                 265                 270

Lys Thr Gly Lys Asp Val Arg Lys Asp Asn Arg Ala Val Gln Lys Leu
        275                 280                 285

Arg Arg Glu Val Glu Lys Ala Lys Arg Ala Leu Ser Ser Gln His Gln
    290                 295                 300

Ala Arg Ile Glu Ile Glu Ser Phe Tyr Glu Gly Glu Asp Phe Ser Glu
305                 310                 315                 320

Thr Leu Thr Arg Ala Lys Phe Glu Glu Leu Asn Met Asp Leu Phe Arg
                325                 330                 335

Ser Thr Met Lys Pro Val Gln Lys Val Leu Glu Asp Ser Asp Leu Lys
            340                 345                 350

Lys Ser Asp Ile Asp Glu Ile Val Leu Val Gly Gly Ser Thr Arg Ile
        355                 360                 365

Pro Lys Ile Gln Gln Leu Val Lys Glu Phe Phe Asn Gly Lys Glu Pro
    370                 375                 380

Ser Arg Gly Ile Asn Pro Asp Glu Ala Val Ala Tyr Gly Ala Ala Val
385                 390                 395                 400

Gln Ala Gly Val Leu Ser Gly Asp Gln Asp Thr Gly Asp Leu Val Leu
                405                 410                 415

Leu Asp Val Cys Pro Leu Thr Leu Gly Ile Glu Thr Val Gly Gly Val
            420                 425                 430

Met Thr Lys Leu Ile Pro Arg Asn Thr Val Val Pro Thr Lys Lys Ser
        435                 440                 445

Gln Ile Phe Ser Thr Ala Ser Asp Asn Gln Pro Thr Val Thr Ile Lys
    450                 455                 460

Val Tyr Glu Gly Glu Arg Pro Leu Thr Lys Asp Asn His Leu Leu Gly
465                 470                 475                 480

Thr Phe Asp Leu Thr Gly Ile Pro Pro Ala Pro Arg Gly Val Pro Gln
                485                 490                 495

Ile Glu Val Thr Phe Glu Ile Asp Val Asn Gly Ile Leu Arg Val Thr
            500                 505                 510

Ala Glu Asp Lys Gly Thr Gly Asn Lys Asn Lys Ile Thr Ile Thr Asn
        515                 520                 525

Asp Gln Asn Arg Leu Thr Pro Glu Glu Ile Glu Arg Met Val Asn Asp
    530                 535                 540

Ala Glu Lys Phe Ala Glu Glu Asp Lys Lys Leu Lys Glu Arg Ile Asp
545                 550                 555                 560

Thr Arg Asn Glu Leu Glu Ser Tyr Ala Tyr Ser Leu Lys Asn Gln Ile
                565                 570                 575

Gly Asp Lys Glu Lys Leu Gly Gly Lys Leu Ser Ser Glu Asp Lys Glu
            580                 585                 590

Thr Met Glu Lys Ala Val Glu Glu Lys Ile Glu Trp Leu Glu Ser His
        595                 600                 605

Gln Asp Ala Asp Ile Glu Asp Phe Lys Ala Lys Lys Lys Glu Leu Glu
    610                 615                 620
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Glu Ile Val Gln Pro Ile Ile Ser Lys Leu Tyr Gly Ser Ala Gly Pro
625 630 635 640

Pro Pro Thr Gly Glu Glu Asp Thr Ala Glu Lys Asp Glu Leu
645 650

<210> SEQ ID NO 73
<211> LENGTH: 493
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

Met Ser Lys Gly Pro Ala Val Gly Ile Asp Leu Gly Thr Thr Tyr Ser
1 5 10 15

Cys Val Gly Val Phe Gln His Gly Lys Val Glu Ile Ile Ala Asn Asp
20 25 30

Gln Gly Asn Arg Thr Thr Pro Ser Tyr Val Ala Phe Thr Asp Thr Glu
35 40 45

Arg Leu Ile Gly Asp Ala Ala Lys Asn Gln Val Ala Met Asn Pro Thr
50 55 60

Asn Thr Val Phe Asp Ala Lys Arg Leu Ile Gly Arg Arg Phe Asp Asp
65 70 75 80

Ala Val Val Gln Ser Asp Met Lys His Trp Pro Phe Met Val Val Asn
85 90 95

Asp Ala Gly Arg Pro Lys Val Gln Val Glu Tyr Lys Gly Glu Thr Lys
100 105 110

Ser Phe Tyr Pro Glu Glu Val Ser Ser Met Val Leu Thr Lys Met Lys
115 120 125

Glu Ile Ala Glu Ala Tyr Leu Gly Lys Thr Val Thr Asn Ala Val Val
130 135 140

Thr Val Pro Ala Tyr Phe Asn Asp Ser Gln Arg Gln Ala Thr Lys Asp
145 150 155 160

Ala Gly Thr Ile Ala Gly Leu Asn Val Leu Arg Ile Ile Asn Glu Pro
165 170 175

Thr Ala Ala Ala Ile Ala Tyr Gly Leu Asp Lys Lys Val Gly Ala Glu
180 185 190

Arg Asn Val Leu Ile Phe Asp Leu Gly Gly Gly Thr Phe Asp Val Ser
195 200 205

Ile Leu Thr Ile Glu Asp Gly Ile Phe Glu Val Lys Ser Thr Ala Gly
210 215 220

Asp Thr His Leu Gly Gly Glu Asp Phe Asp Asn Arg Met Val Asn His
225 230 235 240

Phe Ile Ala Glu Phe Lys Arg Lys His Lys Lys Asp Ile Ser Glu Asn
245 250 255

Lys Arg Ala Val Arg Arg Leu Arg Thr Ala Cys Glu Arg Ala Lys Arg
260 265 270

Thr Leu Ser Ser Ser Thr Gln Ala Ser Ile Glu Ile Asp Ser Leu Tyr
275 280 285

Glu Gly Ile Asp Phe Tyr Thr Ser Ile Thr Arg Ala Arg Phe Glu Glu
290 295 300

Leu Asn Ala Asp Leu Phe Arg Gly Thr Leu Asp Pro Val Glu Lys Ala
305 310 315 320

Leu Arg Asp Ala Lys Leu Asp Lys Ser Gln Ile His Asp Ile Val Leu
325 330 335

Val Gly Gly Ser Thr Arg Ile Pro Lys Ile Gln Lys Leu Leu Gln Asp

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            340                 345                 350

Phe Phe Asn Gly Lys Glu Leu Asn Lys Ser Ile Asn Pro Asp Glu Ala
        355                 360                 365

Val Ala Tyr Gly Ala Ala Val Gln Ala Ala Ile Leu Ser Gly Asp Lys
    370                 375                 380

Ser Glu Asn Val Gln Asp Leu Leu Leu Leu Asp Val Thr Pro Leu Ser
385                 390                 395                 400

Leu Gly Ile Glu Thr Ala Gly Gly Val Met Thr Val Leu Ile Lys Arg
                405                 410                 415

Asn Thr Thr Ile Pro Thr Lys Gln Thr Gln Thr Phe Thr Thr Tyr Ser
            420                 425                 430

Asp Asn Gln Pro Gly Val Leu Ile Gln Val Tyr Glu Gly Glu Arg Ala
        435                 440                 445

Met Thr Lys Asp Asn Asn Leu Leu Gly Lys Phe Glu Leu Thr Gly Met
    450                 455                 460

Pro Gly Gly Met Pro Gly Gly Phe Pro Gly Gly Gly Ala Pro Pro Ser
465                 470                 475                 480

Gly Gly Ala Ser Ser Gly Pro Thr Ile Glu Glu Val Asp
                485                 490


<210> SEQ ID NO 74
<211> LENGTH: 646
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

Met Ser Lys Gly Pro Ala Val Gly Ile Asp Leu Gly Thr Thr Tyr Ser
1               5                   10                  15

Cys Val Gly Val Phe Gln His Gly Lys Val Glu Ile Ile Ala Asn Asp
            20                  25                  30

Gln Gly Asn Arg Thr Thr Pro Ser Tyr Val Ala Phe Thr Asp Thr Glu
        35                  40                  45

Arg Leu Ile Gly Asp Ala Ala Lys Asn Gln Val Ala Met Asn Pro Thr
    50                  55                  60

Asn Thr Val Phe Asp Ala Lys Arg Leu Ile Gly Arg Arg Phe Asp Asp
65                  70                  75                  80

Ala Val Val Gln Ser Asp Met Lys His Trp Pro Phe Met Val Val Asn
                85                  90                  95

Asp Ala Gly Arg Pro Lys Val Gln Val Glu Tyr Lys Gly Glu Thr Lys
            100                 105                 110

Ser Phe Tyr Pro Glu Glu Val Ser Ser Met Val Leu Thr Lys Met Lys
        115                 120                 125

Glu Ile Ala Glu Ala Tyr Leu Gly Lys Thr Val Thr Asn Ala Val Val
    130                 135                 140

Thr Val Pro Ala Tyr Phe Asn Asp Ser Gln Arg Gln Ala Thr Lys Asp
145                 150                 155                 160

Ala Gly Thr Ile Ala Gly Leu Asn Val Leu Arg Ile Ile Asn Glu Pro
                165                 170                 175

Thr Ala Ala Ala Ile Ala Tyr Gly Leu Asp Lys Lys Val Gly Ala Glu
            180                 185                 190

Arg Asn Val Leu Ile Phe Asp Leu Gly Gly Gly Thr Phe Asp Val Ser
        195                 200                 205

Ile Leu Thr Ile Glu Asp Gly Ile Phe Glu Val Lys Ser Thr Ala Gly
    210                 215                 220
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Asp Thr His Leu Gly Gly Glu Asp Phe Asp Asn Arg Met Val Asn His
225                 230                 235                 240

Phe Ile Ala Glu Phe Lys Arg Lys His Lys Lys Asp Ile Ser Glu Asn
                245                 250                 255

Lys Arg Ala Val Arg Arg Leu Arg Thr Ala Cys Glu Arg Ala Lys Arg
            260                 265                 270

Thr Leu Ser Ser Ser Thr Gln Ala Ser Ile Glu Ile Asp Ser Leu Tyr
        275                 280                 285

Glu Gly Ile Asp Phe Tyr Thr Ser Ile Thr Arg Ala Arg Phe Glu Glu
    290                 295                 300

Leu Asn Ala Asp Leu Phe Arg Gly Thr Leu Asp Pro Val Glu Lys Ala
305                 310                 315                 320

Leu Arg Asp Ala Lys Leu Asp Lys Ser Gln Ile His Asp Ile Val Leu
                325                 330                 335

Val Gly Gly Ser Thr Arg Ile Pro Lys Ile Gln Lys Leu Leu Gln Asp
            340                 345                 350

Phe Phe Asn Gly Lys Glu Leu Asn Lys Ser Ile Asn Pro Asp Glu Ala
        355                 360                 365

Val Ala Tyr Gly Ala Ala Val Gln Ala Ala Ile Leu Ser Gly Asp Lys
    370                 375                 380

Ser Glu Asn Val Gln Asp Leu Leu Leu Leu Asp Val Thr Pro Leu Ser
385                 390                 395                 400

Leu Gly Ile Glu Thr Ala Gly Gly Val Met Thr Val Leu Ile Lys Arg
                405                 410                 415

Asn Thr Thr Ile Pro Thr Lys Gln Thr Gln Thr Phe Thr Thr Tyr Ser
            420                 425                 430

Asp Asn Gln Pro Gly Val Leu Ile Gln Val Tyr Glu Gly Glu Arg Ala
        435                 440                 445

Met Thr Lys Asp Asn Asn Leu Leu Gly Lys Phe Glu Leu Thr Gly Ile
    450                 455                 460

Pro Pro Ala Pro Arg Gly Val Pro Gln Ile Glu Val Thr Phe Asp Ile
465                 470                 475                 480

Asp Ala Asn Gly Ile Leu Asn Val Ser Ala Val Asp Lys Ser Thr Gly
                485                 490                 495

Lys Glu Asn Lys Ile Thr Ile Thr Asn Asp Lys Gly Arg Leu Ser Lys
            500                 505                 510

Glu Asp Ile Glu Arg Met Val Gln Glu Ala Glu Lys Tyr Lys Ala Glu
        515                 520                 525

Asp Glu Lys Gln Arg Asp Lys Val Ser Ser Lys Asn Ser Leu Glu Ser
    530                 535                 540

Tyr Ala Phe Asn Met Lys Ala Thr Val Glu Asp Glu Lys Leu Gln Gly
545                 550                 555                 560

Lys Ile Asn Asp Glu Asp Lys Gln Lys Ile Leu Asp Lys Cys Asn Glu
                565                 570                 575

Ile Ile Asn Trp Leu Asp Lys Asn Gln Thr Ala Glu Lys Glu Glu Phe
            580                 585                 590

Glu His Gln Gln Lys Glu Leu Glu Lys Val Cys Asn Pro Ile Ile Thr
        595                 600                 605

Lys Leu Tyr Gln Ser Ala Gly Gly Met Pro Gly Gly Met Pro Gly Gly
    610                 615                 620

Phe Pro Gly Gly Gly Ala Pro Pro Ser Gly Gly Ala Ser Ser Gly Pro
625                 630                 635                 640

Thr Ile Glu Glu Val Asp
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645

<210> SEQ ID NO 75
<211> LENGTH: 188
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

Met Ala Leu Thr Phe Ala Leu Leu Val Ala Leu Leu Val Leu Ser Cys
1 5 10 15

Lys Ser Ser Cys Ser Val Gly Cys Asp Leu Pro Gln Thr His Ser Leu
20 25 30

Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser
35 40 45

Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu
50 55 60

Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His
65 70 75 80

Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser
85 90 95

Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr
100 105 110

Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val
115 120 125

Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys
130 135 140

Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro
145 150 155 160

Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu
165 170 175

Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu
180 185

<210> SEQ ID NO 76
<211> LENGTH: 153
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1 5 10 15

Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu
20 25 30

Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile
35 40 45

Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
50 55 60

Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu
65 70 75 80

Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys
85 90 95

Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile
100 105 110

Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala
115 120 125

Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe

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130 135 140

Cys Gln Ser Ile Ile Ser Thr Leu Thr
145 150

<210> SEQ ID NO 77
<211> LENGTH: 407
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

Met Asp Gly Leu Pro Gly Arg Ala Leu Gly Ala Ala Cys Leu Leu Leu
1 5 10 15

Leu Ala Ala Gly Trp Leu Gly Pro Glu Ala Trp Gly Ser Pro Thr Pro
20 25 30

Pro Pro Thr Pro Ala Ala Pro Pro Pro Pro Pro Pro Pro Gly Ser Pro
35 40 45

Gly Gly Ser Gln Asp Thr Cys Thr Ser Cys Gly Gly Phe Arg Arg Pro
50 55 60

Glu Glu Leu Gly Arg Val Asp Gly Asp Phe Leu Glu Ala Val Lys Arg
65 70 75 80

His Ile Leu Ser Arg Leu Gln Met Arg Gly Arg Pro Asn Ile Thr His
85 90 95

Ala Val Pro Lys Ala Ala Met Val Thr Ala Leu Arg Lys Leu His Ala
100 105 110

Gly Lys Val Arg Glu Asp Gly Arg Val Glu Ile Pro His Leu Asp Gly
115 120 125

His Ala Ser Pro Gly Ala Asp Gly Gln Glu Arg Val Ser Glu Ile Ile
130 135 140

Ser Phe Ala Glu Thr Asp Gly Leu Ala Ser Ser Arg Val Arg Leu Tyr
145 150 155 160

Phe Phe Ile Ser Asn Glu Gly Asn Gln Asn Leu Phe Val Val Gln Ala
165 170 175

Ser Leu Trp Leu Tyr Leu Lys Leu Leu Pro Tyr Val Leu Glu Lys Gly
180 185 190

Ser Arg Arg Lys Val Arg Val Lys Val Tyr Phe Gln Glu Gln Gly His
195 200 205

Gly Asp Arg Trp Asn Met Val Glu Lys Arg Val Asp Leu Lys Arg Ser
210 215 220

Gly Trp His Thr Phe Pro Leu Thr Glu Ala Ile Gln Ala Leu Phe Glu
225 230 235 240

Arg Gly Glu Arg Arg Leu Asn Leu Asp Val Gln Cys Asp Ser Cys Gln
245 250 255

Glu Leu Ala Val Val Pro Val Phe Val Asp Pro Gly Glu Glu Ser His
260 265 270

Arg Pro Phe Val Val Val Gln Ala Arg Leu Gly Asp Ser Arg His Arg
275 280 285

Ile Arg Lys Arg Gly Leu Glu Cys Asp Gly Arg Thr Asn Leu Cys Cys
290 295 300

Arg Gln Gln Phe Phe Ile Asp Phe Arg Leu Ile Gly Trp Asn Asp Trp
305 310 315 320

Ile Ile Ala Pro Thr Gly Tyr Tyr Gly Asn Tyr Cys Glu Gly Ser Cys
325 330 335

Pro Ala Tyr Leu Ala Gly Val Pro Gly Ser Ala Ser Ser Phe His Thr
340 345 350

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Ala Val Val Asn Gln Tyr Arg Met Arg Gly Leu Asn Pro Gly Thr Val
        355                 360                 365

Asn Ser Cys Cys Ile Pro Thr Lys Leu Ser Thr Met Ser Met Leu Tyr
    370                 375                 380

Phe Asp Asp Glu Tyr Asn Ile Val Lys Arg Asp Val Pro Asn Met Ile
385                 390                 395                 400

Val Glu Glu Cys Gly Cys Ala
                405
```

<210> SEQ ID NO 78
<211> LENGTH: 582
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

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Met Ser Pro Ala Pro Arg Pro Pro Arg Cys Leu Leu Leu Pro Leu Leu
1               5                   10                  15

Thr Leu Gly Thr Ala Leu Ala Ser Leu Gly Ser Ala Gln Ser Ser Ser
            20                  25                  30

Phe Ser Pro Glu Ala Trp Leu Gln Gln Tyr Gly Tyr Leu Pro Pro Gly
        35                  40                  45

Asp Leu Arg Thr His Thr Gln Arg Ser Pro Gln Ser Leu Ser Ala Ala
    50                  55                  60

Ile Ala Ala Met Gln Lys Phe Tyr Gly Leu Gln Val Thr Gly Lys Ala
65                  70                  75                  80

Asp Ala Asp Thr Met Lys Ala Met Arg Arg Pro Arg Cys Gly Val Pro
                85                  90                  95

Asp Lys Phe Gly Ala Glu Ile Lys Ala Asn Val Arg Arg Lys Arg Tyr
            100                 105                 110

Ala Ile Gln Gly Leu Lys Trp Gln His Asn Glu Ile Thr Phe Cys Ile
        115                 120                 125

Gln Asn Tyr Thr Pro Lys Val Gly Glu Tyr Ala Thr Tyr Glu Ala Ile
    130                 135                 140

Arg Lys Ala Phe Arg Val Trp Glu Ser Ala Thr Pro Leu Arg Phe Arg
145                 150                 155                 160

Glu Val Pro Tyr Ala Tyr Ile Arg Glu Gly His Glu Lys Gln Ala Asp
                165                 170                 175

Ile Met Ile Phe Phe Ala Glu Gly Phe His Gly Asp Ser Thr Pro Phe
            180                 185                 190

Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Asn
        195                 200                 205

Ile Gly Gly Asp Thr His Phe Asp Ser Ala Glu Pro Trp Thr Val Arg
    210                 215                 220

Asn Glu Asp Leu Asn Gly Asn Asp Ile Phe Leu Val Ala Val His Glu
225                 230                 235                 240

Leu Gly His Ala Leu Gly Leu Glu His Ser Ser Asp Pro Ser Ala Ile
                245                 250                 255

Met Ala Pro Phe Tyr Gln Trp Met Asp Thr Glu Asn Phe Val Leu Pro
            260                 265                 270

Asp Asp Asp Arg Arg Gly Ile Gln Gln Leu Tyr Gly Gly Glu Ser Gly
        275                 280                 285

Phe Pro Thr Lys Met Pro Pro Gln Pro Arg Thr Thr Ser Arg Pro Ser
    290                 295                 300

Val Pro Asp Lys Pro Lys Asn Pro Thr Tyr Gly Pro Asn Ile Cys Asp
305                 310                 315                 320
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Gly Asn Phe Asp Thr Val Ala Met Leu Arg Gly Glu Met Phe Val Phe
325 330 335

Lys Glu Arg Trp Phe Trp Arg Val Arg Asn Asn Gln Val Met Asp Gly
340 345 350

Tyr Pro Met Pro Ile Gly Gln Phe Trp Arg Gly Leu Pro Ala Ser Ile
355 360 365

Asn Thr Ala Tyr Glu Arg Lys Asp Gly Lys Phe Val Phe Phe Lys Gly
370 375 380

Asp Lys His Trp Val Phe Asp Glu Ala Ser Leu Glu Pro Gly Tyr Pro
385 390 395 400

Lys His Ile Lys Glu Leu Gly Arg Gly Leu Pro Thr Asp Lys Ile Asp
405 410 415

Ala Ala Leu Phe Trp Met Pro Asn Gly Lys Thr Tyr Phe Phe Arg Gly
420 425 430

Asn Lys Tyr Tyr Arg Phe Asn Glu Glu Leu Arg Ala Val Asp Ser Glu
435 440 445

Tyr Pro Lys Asn Ile Lys Val Trp Glu Gly Ile Pro Glu Ser Pro Arg
450 455 460

Gly Ser Phe Met Gly Ser Asp Glu Val Phe Thr Tyr Phe Tyr Lys Gly
465 470 475 480

Asn Lys Tyr Trp Lys Phe Asn Asn Gln Lys Leu Lys Val Glu Pro Gly
485 490 495

Tyr Pro Lys Ser Ala Leu Arg Asp Trp Met Gly Cys Pro Ser Gly Gly
500 505 510

Arg Pro Asp Glu Gly Thr Glu Glu Glu Thr Glu Val Ile Ile Ile Glu
515 520 525

Val Asp Glu Glu Gly Gly Gly Ala Val Ser Ala Ala Ala Val Val Leu
530 535 540

Pro Val Leu Leu Leu Leu Leu Val Leu Ala Val Gly Leu Ala Val Phe
545 550 555 560

Phe Phe Arg Arg His Gly Thr Pro Arg Arg Leu Leu Tyr Cys Gln Arg
565 570 575

Ser Leu Leu Asp Lys Val
580

<210> SEQ ID NO 79
<211> LENGTH: 418
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

Met Arg Ala Ala Pro Leu Leu Leu Ala Arg Ala Ala Ser Leu Ser Leu
1 5 10 15

Gly Phe Leu Phe Leu Leu Phe Phe Trp Leu Asp Arg Ser Val Leu Ala
20 25 30

Lys Glu Leu Lys Phe Val Thr Leu Val Phe Arg His Gly Asp Arg Ser
35 40 45

Pro Ile Asp Thr Phe Pro Thr Asp Pro Ile Lys Glu Ser Ser Trp Pro
50 55 60

Gln Gly Phe Gly Gln Leu Thr Gln Leu Gly Met Glu Gln His Tyr Glu
65 70 75 80

Leu Gly Glu Tyr Ile Arg Lys Arg Tyr Arg Lys Phe Leu Asn Glu Ser
85 90 95

Tyr Lys His Glu Gln Val Tyr Ile Arg Ser Thr Asp Val Asp Arg Thr

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            100                 105                 110

Leu Met Ser Ala Met Thr Asn Leu Ala Ala Leu Phe Pro Pro Glu Gly
        115                 120                 125

Val Ser Ile Trp Asn Pro Ile Leu Leu Trp Gln Pro Ile Pro Val His
    130                 135                 140

Thr Val Pro Leu Ser Glu Asp Gln Leu Leu Tyr Leu Pro Phe Arg Asn
145                 150                 155                 160

Cys Pro Arg Phe Gln Glu Leu Glu Ser Glu Thr Leu Lys Ser Glu Glu
                165                 170                 175

Phe Gln Lys Arg Leu His Pro Tyr Lys Asp Phe Ile Ala Thr Leu Gly
            180                 185                 190

Lys Leu Ser Gly Leu His Gly Gln Asp Leu Phe Gly Ile Trp Ser Lys
        195                 200                 205

Val Tyr Asp Pro Leu Tyr Cys Glu Ser Val His Asn Phe Thr Leu Pro
    210                 215                 220

Ser Trp Ala Thr Glu Asp Thr Met Thr Lys Leu Arg Glu Leu Ser Glu
225                 230                 235                 240

Leu Ser Leu Leu Ser Leu Tyr Gly Ile His Lys Gln Lys Glu Lys Ser
                245                 250                 255

Arg Leu Gln Gly Gly Val Leu Val Asn Glu Ile Leu Asn His Met Lys
            260                 265                 270

Arg Ala Thr Gln Ile Pro Ser Tyr Lys Lys Leu Ile Met Tyr Ser Ala
        275                 280                 285

His Asp Thr Thr Val Ser Gly Leu Gln Met Ala Leu Asp Val Tyr Asn
    290                 295                 300

Gly Leu Leu Pro Pro Tyr Ala Ser Cys His Leu Thr Glu Leu Tyr Phe
305                 310                 315                 320

Glu Lys Gly Glu Tyr Phe Val Glu Met Tyr Tyr Arg Asn Glu Thr Gln
                325                 330                 335

His Glu Pro Tyr Pro Leu Met Leu Pro Gly Cys Ser Pro Ser Cys Pro
            340                 345                 350

Leu Glu Arg Phe Ala Glu Leu Val Gly Pro Val Ile Pro Gln Asp Trp
        355                 360                 365

Ser Thr Glu Cys Met Thr Thr Asn Ser His Gln Val Leu Lys Val Ile
    370                 375                 380

Phe Ala Val Ala Phe Cys Leu Ile Ser Ala Val Leu Met Val Leu Leu
385                 390                 395                 400

Phe Ile His Ile Arg Arg Gly Leu Cys Trp Gln Arg Glu Ser Tyr Gly
                405                 410                 415

Asn Ile


<210> SEQ ID NO 80
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

Met Arg Ala Ala Pro Leu Leu Leu Ala Arg Ala Ala Ser Leu Ser Leu
1               5                   10                  15

Gly Phe Leu Phe Leu Leu Phe Phe Trp Leu Asp Arg Ser Val Leu Ala
            20                  25                  30

Lys Glu Leu Lys Phe Val Thr Leu Val Phe Arg His Gly Asp Arg Ser
        35                  40                  45

Pro Ile Asp Thr Phe Pro Thr Asp Pro Ile Lys Glu Ser Ser Trp Pro
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    50                  55                  60

Gln Gly Phe Gly Gln Leu Thr Gln Leu Gly Met Glu Gln His Tyr Glu
65                  70                  75                  80

Leu Gly Glu Tyr Ile Arg Lys Arg Tyr Arg Lys Phe Leu Asn Glu Ser
                85                  90                  95

Tyr Lys His Glu Gln Val Tyr Ile Arg Ser Thr Asp Val Asp Arg Thr
            100                 105                 110

Leu Met Ser Ala Met Thr Asn Leu Ala Ala Leu Phe Pro Pro Glu Gly
        115                 120                 125

Val Ser Ile Trp Asn Pro Ile Leu Leu Trp Gln Pro Ile Pro Val His
    130                 135                 140

Thr Val Pro Leu Ser Glu Asp Gln Leu Leu Tyr Leu Pro Phe Arg Asn
145                 150                 155                 160

Cys Pro Arg Phe Gln Glu Leu Glu Ser Glu Thr Leu Lys Ser Glu Glu
                165                 170                 175

Phe Gln Lys Arg Leu His Pro Tyr Lys Asp Phe Ile Ala Thr Leu Gly
            180                 185                 190

Lys Leu Ser Gly Leu His Gly Gln Asp Leu Phe Gly Ile Trp Ser Lys
        195                 200                 205

Val Tyr Asp Pro Leu Tyr Cys Glu Ser Val His Asn Phe Thr Leu Pro
    210                 215                 220

Ser Trp Ala Thr Glu Asp Thr Met Thr Lys Leu Arg Glu Leu Ser Glu
225                 230                 235                 240

Leu Ser Leu Leu Ser Leu Tyr Gly Ile His Lys Gln Lys Glu Lys Ser
                245                 250                 255

Arg Leu Gln Gly Gly Val Leu Val Asn Glu Ile Leu Asn His Met Lys
            260                 265                 270

Arg Ala Thr Gln Ile Pro Ser Tyr Lys Lys Leu Ile Met Tyr Ser Ala
        275                 280                 285

His Asp Thr Thr Val Ser Gly Leu Gln Met Ala Leu Asp Val Tyr Asn
    290                 295                 300

Gly Leu Leu Pro Pro Tyr Ala Ser Cys His Leu Thr Glu Leu Tyr Phe
305                 310                 315                 320

Glu Lys Gly Glu Tyr Phe Val Glu Met Tyr Tyr Arg Asn Glu Thr Gln
                325                 330                 335

His Glu Pro Tyr Pro Leu Met Leu Pro Gly Cys Ser Pro Ser Cys Pro
            340                 345                 350

Leu Glu Arg Phe Ala Glu Leu Val Gly Pro Val Ile Pro Gln Asp Trp
        355                 360                 365

Ser Thr Glu Cys Met Thr Thr Asn Ser His Gln Gly Thr Glu Asp Ser
    370                 375                 380

Thr Asp
385


<210> SEQ ID NO 81
<211> LENGTH: 646
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

Met Gly Leu Pro Arg Leu Val Cys Ala Phe Leu Leu Ala Ala Cys Cys
1               5                   10                  15

Cys Cys Pro Arg Val Ala Gly Val Pro Gly Glu Ala Glu Gln Pro Ala
            20                  25                  30
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Pro Glu Leu Val Glu Val Glu Val Gly Ser Thr Ala Leu Leu Lys Cys
        35                  40                  45

Gly Leu Ser Gln Ser Gln Gly Asn Leu Ser His Val Asp Trp Phe Ser
    50                  55                  60

Val His Lys Glu Lys Arg Thr Leu Ile Phe Arg Val Arg Gln Gly Gln
65                  70                  75                  80

Gly Gln Ser Glu Pro Gly Glu Tyr Glu Gln Arg Leu Ser Leu Gln Asp
                85                  90                  95

Arg Gly Ala Thr Leu Ala Leu Thr Gln Val Thr Pro Gln Asp Glu Arg
            100                 105                 110

Ile Phe Leu Cys Gln Gly Lys Arg Pro Arg Ser Gln Glu Tyr Arg Ile
        115                 120                 125

Gln Leu Arg Val Tyr Lys Ala Pro Glu Glu Pro Asn Ile Gln Val Asn
    130                 135                 140

Pro Leu Gly Ile Pro Val Asn Ser Lys Glu Pro Glu Glu Val Ala Thr
145                 150                 155                 160

Cys Val Gly Arg Asn Gly Tyr Pro Ile Pro Gln Val Ile Trp Tyr Lys
                165                 170                 175

Asn Gly Arg Pro Leu Lys Glu Glu Lys Asn Arg Val His Ile Gln Ser
            180                 185                 190

Ser Gln Thr Val Glu Ser Ser Gly Leu Tyr Thr Leu Gln Ser Ile Leu
        195                 200                 205

Lys Ala Gln Leu Val Lys Glu Asp Lys Asp Ala Gln Phe Tyr Cys Glu
    210                 215                 220

Leu Asn Tyr Arg Leu Pro Ser Gly Asn His Met Lys Glu Ser Arg Glu
225                 230                 235                 240

Val Thr Val Pro Val Phe Tyr Pro Thr Glu Lys Val Trp Leu Glu Val
                245                 250                 255

Glu Pro Val Gly Met Leu Lys Glu Gly Asp Arg Val Glu Ile Arg Cys
            260                 265                 270

Leu Ala Asp Gly Asn Pro Pro Pro His Phe Ser Ile Ser Lys Gln Asn
        275                 280                 285

Pro Ser Thr Arg Glu Ala Glu Glu Glu Thr Thr Asn Asp Asn Gly Val
    290                 295                 300

Leu Val Leu Glu Pro Ala Arg Lys Glu His Ser Gly Arg Tyr Glu Cys
305                 310                 315                 320

Gln Gly Leu Asp Leu Asp Thr Met Ile Ser Leu Leu Ser Glu Pro Gln
                325                 330                 335

Glu Leu Leu Val Asn Tyr Val Ser Asp Val Arg Val Ser Pro Ala Ala
            340                 345                 350

Pro Glu Arg Gln Glu Gly Ser Ser Leu Thr Leu Thr Cys Glu Ala Glu
        355                 360                 365

Ser Ser Gln Asp Leu Glu Phe Gln Trp Leu Arg Glu Glu Thr Gly Gln
    370                 375                 380

Val Leu Glu Arg Gly Pro Val Leu Gln Leu His Asp Leu Lys Arg Glu
385                 390                 395                 400

Ala Gly Gly Gly Tyr Arg Cys Val Ala Ser Val Pro Ser Ile Pro Gly
                405                 410                 415

Leu Asn Arg Thr Gln Leu Val Asn Val Ala Ile Phe Gly Pro Pro Trp
            420                 425                 430

Met Ala Phe Lys Glu Arg Lys Val Trp Val Lys Glu Asn Met Val Leu
        435                 440                 445

Asn Leu Ser Cys Glu Ala Ser Gly His Pro Arg Pro Thr Ile Ser Trp
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    450                 455                 460

Asn Val Asn Gly Thr Ala Ser Glu Gln Asp Gln Asp Pro Gln Arg Val
465                 470                 475                 480

Leu Ser Thr Leu Asn Val Leu Val Thr Pro Glu Leu Leu Glu Thr Gly
                485                 490                 495

Val Glu Cys Thr Ala Ser Asn Asp Leu Gly Lys Asn Thr Ser Ile Leu
            500                 505                 510

Phe Leu Glu Leu Val Asn Leu Thr Thr Leu Thr Pro Asp Ser Asn Thr
        515                 520                 525

Thr Thr Gly Leu Ser Thr Ser Thr Ala Ser Pro His Thr Arg Ala Asn
    530                 535                 540

Ser Thr Ser Thr Glu Arg Lys Leu Pro Glu Pro Glu Ser Arg Gly Val
545                 550                 555                 560

Val Ile Val Ala Val Ile Val Cys Ile Leu Val Leu Ala Val Leu Gly
                565                 570                 575

Ala Val Leu Tyr Phe Leu Tyr Lys Lys Gly Lys Leu Pro Cys Arg Arg
            580                 585                 590

Ser Gly Lys Gln Glu Ile Thr Leu Pro Pro Ser Arg Lys Ser Glu Leu
        595                 600                 605

Val Val Glu Val Lys Ser Asp Lys Leu Pro Glu Glu Met Gly Leu Leu
    610                 615                 620

Gln Gly Ser Ser Gly Asp Lys Arg Ala Pro Gly Asp Gln Gly Glu Lys
625                 630                 635                 640

Tyr Ile Asp Leu Arg His
                645


<210> SEQ ID NO 82
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 82

Thr Lys Ala Gly Arg Gly Ala Ser Gln Pro Pro Thr Pro Thr Pro Ala
1               5                   10                  15

Ser Asp Ala Phe
            20


<210> SEQ ID NO 83
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 83

Glu Glu Glu Pro Glu Glu Thr Ala Glu Asp Thr Thr Glu Asp Thr Glu
1               5                   10                  15

Gln Asp Glu Asp
            20


<210> SEQ ID NO 84
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 84
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Thr Ala Ser Thr Thr Ala Asn Thr Pro Phe Pro Thr Ala Thr Ser Pro
1 5 10 15

Ala Pro Pro Ile
20

<210> SEQ ID NO 85
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 85

Pro Ala Pro Pro Ile Ile Ser Thr His Ser Ser Ser Thr Ile Pro Thr
1 5 10 15

Pro Ala Pro Pro
20

<210> SEQ ID NO 86
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 86

Leu Ala Lys Met Tyr Tyr Ser Ala Val Glu Pro Thr Lys Asp Ile Phe
1 5 10 15

Thr Gly Leu Ile
20

<210> SEQ ID NO 87
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 87

Pro Ser Ser Thr Lys Pro Pro Ala Leu Ser His Ser Val Ser Thr Ser
1 5 10 15

Ser Thr Thr Lys
20

<210> SEQ ID NO 88
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 88

Leu Glu Pro Asp Tyr Phe Lys Asp Met Thr Pro Thr Ile Arg Lys Thr
1 5 10 15

Gln Lys Ile Val
20

<210> SEQ ID NO 89
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

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<400> SEQUENCE: 89

Ser Thr Met Pro Val Val Ser Ser Glu Ala Ser Thr His Ser Thr Thr
1 5 10 15

Pro Val Asp Thr
20

<210> SEQ ID NO 90
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 90

Ser Thr His Ser Thr Thr Pro Val Asp Thr Ser Thr Pro Val Thr Thr
1 5 10 15

Ser Thr Glu Ala
20

<210> SEQ ID NO 91
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 91

Ile Pro Pro Glu Asp Thr Ala Ser Thr Arg Ser Ser Phe Thr Val Gln
1 5 10 15

Asp Leu Lys Pro
20

<210> SEQ ID NO 92
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 92

Glu Ala Lys Thr Ser Asn Pro Thr Ser Ser Leu Thr Ser Leu Ser Val
1 5 10 15

Ala Pro Thr Phe
20

<210> SEQ ID NO 93
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 93

Ala Arg Thr Glu Pro Trp Glu Gly Asn Ser Ser Thr Ala Ala Thr Thr
1 5 10 15

Pro Glu Thr Phe
20

<210> SEQ ID NO 94
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

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<400> SEQUENCE: 94

Val Asp Pro Leu Gln Leu Gln Thr Pro Pro Gln Thr Gln Pro Gly Pro
1 5 10 15

Ser His Val Met
20

<210> SEQ ID NO 95
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 95

Ser Pro Lys Pro Ser Thr Thr Asn Val Phe Thr Ser Ala Val Asp Gln
1 5 10 15

Thr Ile Thr Pro
20

<210> SEQ ID NO 96
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 96

Pro Ala Pro Pro Ala Pro Gly Asn Ala Ser Glu Ser Glu Glu Asp Arg
1 5 10 15

Ser Ala Gly Ser
20

<210> SEQ ID NO 97
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 97

Ala Ser Glu Ser Glu Glu Asp Arg Ser Ala Gly Ser Val Glu Ser Pro
1 5 10 15

Ser Val Ser Ser
20

<210> SEQ ID NO 98
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 98

Ala Asn Leu Asn Ser Asp Lys Glu Asn Ile Thr Thr Ser Asn Leu Lys
1 5 10 15

Ala Ser His Ser
20

<210> SEQ ID NO 99
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 99

Leu Thr Thr Asn Ser Asp Ser Phe Thr Gly Phe Thr Pro Tyr Gln Glu
1 5 10 15

Lys Thr Thr Leu
20

<210> SEQ ID NO 100
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 100

Ser Phe Thr Gly Phe Thr Pro Tyr Gln Glu Lys Thr Thr Leu Gln Pro
1 5 10 15

Thr Leu Lys Phe
20

<210> SEQ ID NO 101
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 101

Ser Phe Thr Gly Phe Thr Pro Tyr Gln Glu Lys Thr Thr Leu Gln Pro
1 5 10 15

Thr Leu Lys Phe
20

<210> SEQ ID NO 102
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 102

Ser Pro Thr Ser Ser Ala Ser Ser Phe Ser Ser Ser Ala Pro Phe Leu
1 5 10 15

Ala Ser Ala Val
20

<210> SEQ ID NO 103
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 103

Thr Val Pro Cys Pro Val Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser
1 5 10 15

Thr Pro Pro Thr
20

<210> SEQ ID NO 104
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 104

Val Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser Thr Pro Pro Thr Pro
1 5 10 15

Ser Pro Ser Cys
20

<210> SEQ ID NO 105
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 105

Ser Glu Pro Pro Lys Ala Ala Arg Pro Pro Val Thr Pro Val Leu Leu
1 5 10 15

Glu Lys Lys Ser
20

<210> SEQ ID NO 106
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 106

Gly Gln Ser Gln Pro Thr Val Ala Gly Gln Pro Ser Ala Arg Pro Ala
1 5 10 15

Ala Glu Glu Tyr
20

<210> SEQ ID NO 107
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 107

Thr Pro Ala Ser Ile Thr Ala Ala Lys Thr Ser Thr Ile Thr Thr Ala
1 5 10 15

Phe Pro Pro Val
20

<210> SEQ ID NO 108
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 108

Gly Asn Ala Ser Met Asp Ala Val Cys Thr Ser Thr Ser Pro Thr Arg
1 5 10 15

Ser Met Ala Pro
20

<210> SEQ ID NO 109
<211> LENGTH: 20
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 109

Thr Asp Cys Gly Gly Pro Lys Asp His Pro Leu Thr Cys Asp Asp Pro
1 5 10 15

Arg Phe Gln Ala
20

<210> SEQ ID NO 110
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 110

Ala Gln Ala Ser Ser Ser Ser Lys Ala Pro Pro Pro Ser Leu Pro Ser
1 5 10 15

Pro Ser Arg Leu Pro
20

<210> SEQ ID NO 111
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 111

Pro Leu Ser Glu Leu Glu Ser Gly Glu Gln Pro Ser Asp Glu Gln Pro
1 5 10 15

Ser Gly Glu His
20

<210> SEQ ID NO 112
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 112

Pro Gln Arg Ser Ser Thr Ala Ile Leu Gln Val Ser Val Thr Asp Thr
1 5 10 15

Asn Asp Asn His
20

<210> SEQ ID NO 113
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 113

Gly Ala Leu Pro Gly Thr Ser Val Met Glu Val Thr Ala Thr Asp Ala
1 5 10 15

Asp Asp Asp Val
20

<210> SEQ ID NO 114
<211> LENGTH: 20

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 114

Glu Gln Glu Pro Pro Ser Thr Asp Val Pro Pro Ser Pro Glu Ala Gly
1 5 10 15

Gly Thr Thr Gly
20

<210> SEQ ID NO 115
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 115

Arg Pro Glu Ala Thr Pro Phe Leu Val Ala His Thr Arg Thr Arg Pro
1 5 10 15

Pro Ser Gly Gly
20

<210> SEQ ID NO 116
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 116

Pro Gly Thr Ser Thr Thr Pro Ser Gln Pro Asn Ser Ala Gly Val Gln
1 5 10 15

Asp Thr Glu Met
20

<210> SEQ ID NO 117
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 117

Glu Val Ala Pro Glu Ala Ser Thr Ser Ser Ala Ser Gln Val Ile Ala
1 5 10 15

Pro Thr Gln Val
20

<210> SEQ ID NO 118
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 118

Gln Pro Pro Asp Phe Ala Leu Ala Tyr Arg Pro Ser Phe Pro Glu Asp
1 5 10 15

Arg Glu Pro Gln
20

<210> SEQ ID NO 119

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<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 119

Leu Ser Val Thr Arg Pro Val Val Val Ser Ala Thr His Pro Thr Leu
1 5 10 15

Pro Ser Ala His
20

<210> SEQ ID NO 120
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 120

Pro Ser Ala His Gln Pro Pro Val Ile Pro Ala Thr His Pro Ala Leu
1 5 10 15

Ser Arg Asp His
20

<210> SEQ ID NO 121
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 121

Ala Pro Asp Ala Leu Val Leu Arg Thr Gln Ala Thr Gln Leu Pro Ile
1 5 10 15

Ile Pro Thr Ala
20

<210> SEQ ID NO 122
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 122

Gly Ala Leu Phe Pro Gly Pro Gly Asn Ala Gln Thr Ser Val Ser Pro
1 5 10 15

Ser Lys Val Ile
20

<210> SEQ ID NO 123
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 123

His Leu Ala Leu Gly Asp Gln Arg Leu Asn Pro Thr Val Thr Tyr Gly
1 5 10 15

Asn Asp Ser Phe
20

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<210> SEQ ID NO 124
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 124

His Leu Ala Leu Gly Asp Gln Arg Leu Asn Pro Thr Val Thr Tyr Gly
1 5 10 15

Asn Asp Ser Phe
20

<210> SEQ ID NO 125
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 125

Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp
1 5 10 15

Val Thr Ser Val
20

<210> SEQ ID NO 126
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 126

Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His
1 5 10 15

Asp Val Thr Ser
20

<210> SEQ ID NO 127
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 127

Asn Val Thr Ser Ala Ser Gly Ser Ala Ser Gly Ser Ala Ser Thr Leu
1 5 10 15

Val His Asn Gly
20

<210> SEQ ID NO 128
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 128

Asn Val Thr Ser Ala Ser Gly Ser Ala Ser Gly Ser Ala Ser Thr Leu
1 5 10 15

Val His Asn Gly
20

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<210> SEQ ID NO 129
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 129

Gly Thr Ser Ala Arg Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro
1 5 10 15

Phe Ser Ile Pro
20

<210> SEQ ID NO 130
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 130

Gly Thr Ser Ala Arg Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro
1 5 10 15

Phe Ser Ile Pro
20

<210> SEQ ID NO 131
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 131

Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys Thr Asp Ala
1 5 10 15

Ser Ser Thr His
20

<210> SEQ ID NO 132
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 132

Thr Lys Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu
1 5 10 15

Thr Ser Ser Asn
20

<210> SEQ ID NO 133
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 133

Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu
1 5 10 15

Gln Ile Tyr Lys
20

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<210> SEQ ID NO 134
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 134

His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser
1 5 10 15

Arg Tyr Asn Leu
20

<210> SEQ ID NO 135
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 135

Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val
1 5 10 15

Pro Phe Pro Phe
20

<210> SEQ ID NO 136
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 136

Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val Pro Phe
1 5 10 15

Pro Phe Ser Ala
20

<210> SEQ ID NO 137
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 137

Asp Val Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly
1 5 10 15

Ala Gly Val Pro
20

<210> SEQ ID NO 138
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 138

Thr Ala Gly Arg Pro Thr Gly Gln Ser Ser Pro Thr Ser Pro Ser Ala
1 5 10 15

Ser Pro Gln Glu

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20

<210> SEQ ID NO 139
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 139

Ser Leu Ala Ser Gln Ala Thr Asp Thr Phe Ser Thr Val Pro Pro Thr
1 5 10 15

Pro Pro Ser Ile
20

<210> SEQ ID NO 140
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 140

Phe Ser Thr Val Pro Pro Thr Pro Pro Ser Ile Thr Ser Thr Gly Leu
1 5 10 15

Thr Ser Pro Gln
20

<210> SEQ ID NO 141
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 141

Pro Thr Pro Pro Ser Ile Thr Ser Thr Gly Leu Thr Ser Pro Gln Thr
1 5 10 15

Glu Thr His Thr
20

<210> SEQ ID NO 142
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 142

Leu Thr Ser Pro Gln Thr Glu Thr His Thr Leu Ser Pro Ser Gly Ser
1 5 10 15

Gly Lys Thr Phe
20

<210> SEQ ID NO 143
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 143

Thr Asp Thr Ser Ser Ala Ser Thr Gly His Ala Thr Pro Leu Pro Val
1 5 10 15

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Thr Ser Leu Ser
20

<210> SEQ ID NO 144
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 144

His Ala Thr Pro Leu Ala Val Ser Ser Ala Thr Ser Ala Ser Thr Val
1 5 10 15

Ser Ser Asp Ser
20

<210> SEQ ID NO 145
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 145

Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His
1 5 10 15

Asp Val Thr Ser
20

<210> SEQ ID NO 146
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 146

Ser Leu Ala Ser Gln Ala Thr Asp Thr Phe Ser Thr Val Pro Pro Thr
1 5 10 15

Pro Pro Ser Ile
20

What is claimed is:

1. A panel of glycopeptides comprising at least a plurality of isolated glycopeptides, each isolated glycopeptide comprising a glycopeptide epitope, said epitope having been previously determined (i) to be selectively recognized by a subset of antibodies in sera from cancer patients, which subset recognizes neither (a) the corresponding naked peptides of said panel when not glycosylated; nor (b) the corresponding glycan when not bound to said peptide; and (ii) not to be recognized by antibodies in control sera, said plurality comprising at least 8 isolated glycopeptides, wherein said plurality comprises isolated glycopeptides comprising amino acid sequences of SEQ ID NOs: 86, 109, 116, 132, 134, 135, 145, and 146, wherein said glycopeptides are immobilized on said panel.

2. The panel of glycopeptides of claim **1**, wherein the plurality of isolated glycopeptides comprises SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQPNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVSDVPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPPSI (SEQ ID NO: 146).

3. The panel of glycopeptides of claim **1**, wherein the plurality comprises at least 8 and up to 30 isolated glycopeptides, wherein the plurality comprises isolated glycopeptides having amino acid sequences SEQ ID NOs: 86, 109, 116, 132, 134, 135, 145, and 146.

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